vol. 24
número
36

revista brasileira de cancerologia

revista brasileira de cancerologia

VIII — ÊSTE NÚMERO
Simpósio Internacional sôbre Doença de Hodgkin
Editado por M. Santos-Silva

Volume 24 — Abril, 1968 — Número 36

REVISTA BRASILEIRA DE CANCEROLOGIA

Publicação trimestral de distribuição gratuita às instituições médicas do País e do Estrangeiro e aos médicos em geral, de acôrdo com o critério dos editôres.

Solicita-se permuta com Revistas Médicas.

SERVIÇO NACIONAL DE CÂNCER
SECÇÃO DE ORGANIZAÇÃO E CONTRÔLE
Praça Cruz Vermelha, 23 - 3.º andar
RIO DE JANEIRO — BRASIL

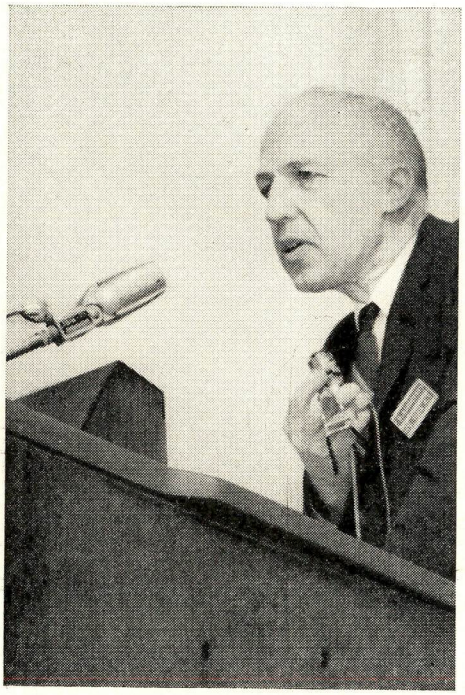
SIMPÓSIO INTERNACIONAL SÔBRE DOENÇA DE HODGKIN

REALIZADO NO INSTITUTO NACIONAL DE CÂNCER

Rio de Janeiro — 16 a 20 de Janeiro de 1967

ÍNDICE DA MATÉRIA

Êste número da Revista Brasileira de Cancerologia foi editado pelo *Dr. Moacyr Santos-Silva,* que contou com a valiosa colaboração dos *Drs. César Lima Santos* e *J. E. Ultmann.*



Êste número especial da Revista Brasileira de Cancerologia é editado em homenagem ao Dr. David A. Karnofsky.

Muito deve a cancerologia, principalmente a cancerologia médica, a David A. Karnofsky. Sua incansável atividade no campo da quimioterapia, experimental e clínica, tem contribuído de forma contínua para tornar êste tipo de tratamento cada vez mais racional. A metodologia que propôs para avaliar os resultados do tratamento médico do câncer tende a ter aceitação universal. Na realidade, não se pode falar em oncologia médica sem, a cada passo, referir ao que ensinou e continua ensinando.

Ao prestar-lhe esta homenagem queremos ressaltar, também, sua impressionante figura humana que torna mais admirável ainda o grande mérito científico de David A. Karnofsky.

O EDITOR

RELAÇÃO DOS PARTICIPANTES

ALAN C. AISENBERG

Assistant Physician, Massachusetts General Hospital; Assistant Professor of Medicine, Harvard Medical School, Boston, Massachusetts.

JCSEPH H. BURCHENAL

Vice President, Sloan-Kettering Institute for Cancer Research; Associate Medical Director for Clinical Investigation and Attending Physician,, Memorial Hospital; Professor of Medicine, Cornell University Medical College, New York, N. Y.

HENRY S. KAPLAN

Professor and Executive, Department, of Radiology - Stanford University School of Medicine, Palo Alto, California.

DAVID A. KARNOFSKY

Attending Physician and Chief, Medical Oncology Service, Department of Medicine, Memorial Hospital; Chief, Division of Clinical Chemotherapy, Sloan-Kettering Institute; Professor of Medicine, Cornell University Medical College, New York, N. Y.

ROBERT J. LUKES

Professor of Pathology, University of Southern California School of Medicine and the Los Angeles County Hospital, Los Angeles California.

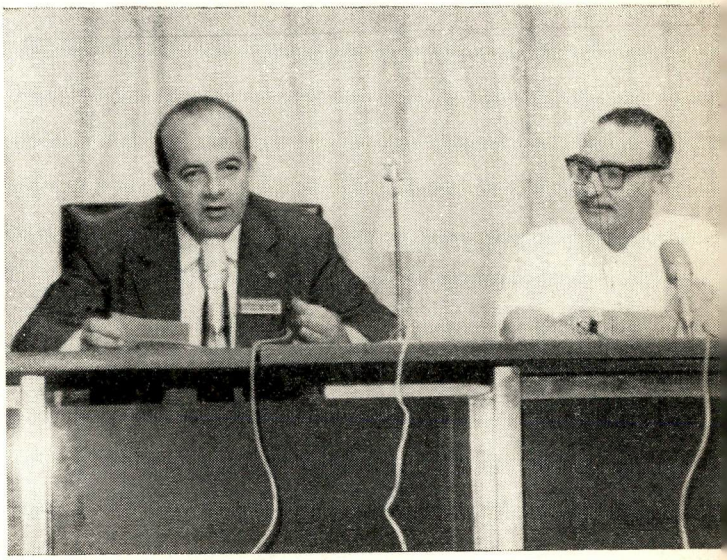
M. VERA PETERS

Head, Radiology Department from the Ontario Cancer Institute Incorporating the Princess Margaret Hospital, Toronto, Canada.

JOHN E. ULTMANN

Assistant Professor of Medicine, College of Physicians and Surgeons, Columbia University; Visiting Physician, the Francis Delafield Hospital, New York, N. Y.

OPENING REMARKS



DR. MOACYR SANTOS - SILVA
Director, Serviço Nacional de Câncer
1963-1967

Rio de Janeiro, Brasil

Mr. Chairman, participants of this Symposium, my colleagues of the "Instituto de Câncer", guest physicians :

It is an honor for me to extend a welcome to Brazil to the distinguished participants of this symposium. I shall not try to enumerate the merits and achievements of each in the field of oncology because their names are well know. As men devoted to progress of medicine and interested in the welfare of mankind none of them hesitated to commit themselves to come such a long way to discuss the changing concepts and the new approach of the management of the patient with Hodgkin's disease.

As a matter of fact, for the last few years, as new data was accrued, the possibility of cure for patients with Hodgkin's disease was predicted and became a central point of interest for the medical oncologist and the radiotherapist. Strong evidence supports the concept that Hodgkin's disease may start in a single tissue area and may follow a predictable and orderly progression, thus justifying a radical approach to radiation therapy using extended fields for the treatment of the adjacent areas as will be discussed by Dr. Kaplan and Dr. Peters. As it was once stated, "ideas and concepts can be grasped quite quickly, but often one requires further information on the underlying technics". In our particular case, and considering that this meeting is not a formal one, we would like to have Dr. Kaplan and Dr. Peters discuss the technical details of their approach to radical radiation therapy.

The routine application of lymphoadenography in the preliminary clinical evaluation of the patient with Hodgkin's disease suggests the possibility that, "ab initio", this disease, in some instances may have a multicentric origin. Dr. Ultmann will review the natural history and Dr. Robert Lukes in discussing his useful pathological classification of Hodgkin's disease will certainly clarify this point. The differences in histologic pattern presented by this disease are baffling and often times makes one wonder if all its variants represent true neoplastic disease. We may also add that the microscopic diagnosis of Hodgkin's disease is not always clear-cut even for the experienced pathologists. We want to have Professor Lukes settle the criteria that govern the establishment of the pathological diagnosis of Hodgkin's disease in the absence of typi-

cal Reed-Sternberg cells if this is at all possible.

The study of the immunologic defects presented by these patients and the fluctuation of the anergic status in the course of the disease may lead to very important developments in understanding the pathophysiology, and, possibly, the etiology of the disease. Dr. Aisenberg will refer to its present day importance and future implications.

The etiology of Hodgkin's disease remains obscure at the present time. Dr. Burchenal during his appraisal of Burkitt's tumor will have the opportunity to develop this topic, since the study of the African lymphoma may add a great deal to the understanding of Hodgkin's disease and the other lymphomas and leukemias, as well. We are also eager to hear Dr. Lukes discuss Burkitt's tumor from the pathological point of view. Is Burkitt's tumor an autonomous pathological entity or does it represent a clinical variant of lymphosarcoma when it occurs in children?

Dr. Karnofsky will examine an extremely important and controversial aspect of medical oncology. What is the role of chemotherapy in the treatment of the Hodgkin's disease patient? Is it at all permissible to use any of the available drugs in treating stage I and II Hodgkin's disease in place of radiation therapy? Must chemotherapy be the sole treatment for stages III and IV Hodgkin's disease? Should chemotherapy be decentralized and practiced by any physician?

We will have a very challenging program this week. All these questions and the many others that will be asked by the audience will, I hope, stimulate much discussion. For the formal presentations and answers to the many questions, we would like to express our indebtness to our very distinguished guests who have honored us by accepting our invitation.

In closing, I want to aknowledge the financial support that the Brazilian Minister of Health — Dr. Raymundo de Britto — gave to the Cancer Institute to develop this program. His breadth and comprehension made possible not only this symposium but also this new phase of the Rio de Janeiro Cancer Institute. In a few more days this new 8.000 square meter building will be fully in operation. It is indeed a very beautiful and comfortable building. But our main concern is not esthetic. The opening of this auditorium with this meeting denotes that this hospital will not be known only by its setting of bricks and mortar. An everlasting echoing of this week's activities will remain inside its walls as a propelling impetus and inspiration to scientific work and as a stimulus toward attaining new goals in the fight against cancer in Brasil.

Again, the warmest welcome to our guests who came from abroad and to all of you.

To Professor Francisco Fialho, the director of the Cancer Institute, I want to express my profound gratitude. His continuing help and enthusiasm made possible the development of this hospital and the promise we can make to our young colleagues: the Cancer Institute will always be pioneering Brazilian oncology.

CONSIDERAÇÕES PRELIMINARES

DR. MOACYR SANTOS - SILVA

Diretor do Serviço Nacional de Câncer
1963-1967

Rio de Janeiro, Brasil

Senhor Coordenador, participantes dêste Symposium, médicos do Instituto de Câncer e convidados:

É uma honra dar as boas vindas aos ilustres participantes dêste Symposium. Não procuraremos enumerar os méritos nem as contribuições que cada um dêles deu à oncologia, pois, todos nós aqui reunidos os conhecemos muito bem. Homens devotados que são ao progresso da medicina e interessados no bem estar da humanidade não hesitaram em dar esta longa caminhada para discutir os novos conceitos e a atual filosofia que governa o tratamento do doente portador de doença de Hodgkin.

Como é de conhecimento geral, nos últimos anos, à medida que foram coligidos novos fatos, a possibilidade de cura para o doente portador de doença de Hodgkin surgiu como uma possibilidade, passando a ser o ponto central do interêsse do oncologista médico e do radioterapêuta. Uma série de observações dão apoio ao conceito que estabelece que a doença de Hodgkin pode começar em um único ponto, podendo propagar-se de forma previsível e ordenada, justificando o tratamento radical pelas irradiações através de campos extensos e o tratamento das áreas adjacentas, como será aqui apresentado pelo Dr. Kaplan e pela Dra. Vera Peters. Como já disse alguém, "as idéias e os conceitos podem ser ràpidamente aprendidos, porém, muitas vêzes, é necessário que sejam dadas informações adicionais referentes às técnicas". Neste caso particular, e considerando que êste Symposium é educativo, gostaríamos que o Dr. Kaplan e a Dra. Peters, discutissem as minúcias técnicas relativas ao tratamento radical com as irradiações.

O emprêgo rotineiro da linfoangiodenografia na avaliação clínica preliminar do doente com doença de Hodgkin sugere a possibilidade de, desde o início, ser essa doença, em alguns casos, de origem multicêntrica. O Dr. Ultmann fará aqui a revisão da história natural desta doença e o Dr. Robert Lukes, quando discutir a sua muito útil classificação patológica irá, certamente, esclarecer êste ponto. As diferenças do componente histológico apresentado pela doença de Hodgkin é desnorteante e, freqüentemente, faz que surjam dúvidas: tôdas as variantes histológicas representam doença neoplásica verdadeira? Podemos, também, acrescentar que o diagnóstico microscópico da

doença de Hodgkin nem sempre é fácil, mesmo quando o estudo é feito por patologistas experientes. Gostaríamos que o Professor Robert Lukes estabelecesse o critério que governa o diagnóstico patológico da doença de Hodgkin quando não existem células típicas de Reed-Sternberg.

O estudo dos defeitos imunológicos apresentados por êsses pacientes e a flutuação do estado anérgico no curso da doença pode conduzir à compreensão da fisiopatologia e possìvelmente da etiologia desta doença. O Dr. Aisenberg apresentará o assunto e fará referências à importância atual e às futuras implicações do que se observa em relação ao estado imunológico nos doentes portadores da doença de Hodgkin.

A etiologia da doença de Hodgkin continua obscura. O Dr. Burchenal durante sua apreciação sôbre o tumor de Burkitt terá a oportunidade de desenvolver êste tópico, uma vez que o estudo do linfoma Africano pode acrescentar muito para a compreensão da doença de Hodgkin e dos outros linfomas e leucemias. Temos também muito interêsse em ouvir o Dr. Lukes abordar os aspectos referentes à patologia do linfoma de Burkitt. Será êsse tumor uma entidade patológica autônoma, ou representa uma variante clínica de linfossarcoma que acomete as crianças?

O Dr. Karnofsky examinará um aspecto muito importante e extremamente controvertido da oncologia médica: o papel da quimioterapia no tratamento do doente com doença de Hodgkin. Será racional usar as drogas presentemente conhecidas no tratamento dos estágios I e II desta doença, em lugar do tratamento com as irradiações? Deve a quimioterapia ser o único tratamento para os estádios III e IV? É recomendável que a quimioterapia seja descentralizada e praticada por qualquer médico?

Esta semana teremos um programa extremamente estimulante. Tôdas estas perguntas e muitas outras que serão feitas pelos médicos que assistem a êste Symposium virão, esperamos, estimular muita discussão. Pelas apresentações formais e pelas respostas às muitas questões que serão formuladas queremos neste momento expressar aos eminentes convidados nosso agradecimento e, também, mais uma vez agradecer-lhes por nos ter honrado aceitando nosso convite.

Antes de terminar queremos fazer um agradecimento público ao Exmo. Sr. Ministro da Saúde — Dr. Raymundo de Brito — pelo apoio financeiro e pelo estímulo que deu ao Serviço Nacional de Câncer para organizar êste Symposium. Sua ampla visão e compreensão tornaram possível não sòmente a realização desta reunião mas, também, permitiram que o Instituto Nacional de Câncer chegasse a esta nova fase de desenvolvimento. Dentro de poucos dias mais todo êsse nôvo edifício, com 8.000 metros quadrados, estará em pleno funcionamento. Trata-se, na realidade, de um belo e confortável edifício. Porém, nossa maior preocupação não é a estética. A abertura dêste auditório, com esta reunião, denota que êste hospital não será no futuro conhecido apenas pelo arranjo de seus tijolos e argamaça. O eco que perdurará das atividades desta semana continuará a ressoar como um ímpeto e uma inspiração para o trabalho científico e como um estímulo para novas realizações na luta contra o câncer no Brasil.

Mais uma vez apresento aos ilustres membros dêste Symposium e a todos que aqui estão presentes sinceros votos de boas vindas.

Ao Professor Francisco Fialho, Diretor do Instituto Nacional de Câncer, queremos expressar nossa gratidão profunda. Seu auxílio continuado e seu entusiasmo tornaram possível o desenvolvimento dêste hospital e a promessa que podemos fazer aos nossos jovens colegas: o Instituto Nacional de Câncer continuará sempre pioneiro na oncologia Brasileira.

CLINICAL ASPECTS AND DIAGNOSIS OF HODGKIN'S DISEASE

DR. JOHN E. ULTMANN

Hodgkin's disease is a complex pathologic entity involving one or more lymph nodes and, often, other organs with a wide variety of clinical manifestations. Even though it has been 135 years since Hodgkin first described this disorder, the etiology of the disease has not yet been elucidated. In 1865, Wilks further delineated the syndrome and named the disease with Hodgkin's name. In 1870, Murchison described the first patient with fever and Hodgkin's disease, but it was not until 1900 that Pell and Epstein delineated the fever characteristic of this illness. The credit for separating Hodgkin's disease histologically from the other lymphomata must go to Sternberg and Reed who, in 1898 and 1902, respectively, described the histologic picture which characterizes Hodgkin's disease.

The current interest in Hodgkin's disease stems first from the fact that clinical observations together with recently developed laboratory techniques now permit greater understanding of the pathophysiology than was previously possible and, second, that new therapeutic approaches are now available which promise to extend useful life in many patients and to cure some.

Incidence

In the United States of America, each year approximately 3200 deaths are due to Hodgkin's disease. Incidence rates are somewhat higher than mortality rates; the difference is probably due to the substantial portion of persons with Hodgkin's disease who live long enough to have their deaths attributed to other causes. The incidence of the lymphomata appears to be rising in Europe and in the Americas. In contrast to the experience in Western countries, the Chinese of Hong Kong, the Koreans and the Japonese have a distinct absence of lymphomata in general and of Hodgkin's disease in particular. Although rare, the most common lymphoma in the Orient is reticulum cell sarcoma.

Unlike lymphosarcoma and reticulum cell sarcoma, Hodgkin's disease has a characteristically bi-modal curve, with the first mode between 15 and the second mode at over 50 years of age. Fifty-eight to sixty-six per cent of Hodgkin's disease patients are male. The bi-modality by age is exhibited in both sexes. Mortality data show fewer females in the 15 to 34 year age group than is apparent in the incidence data. The explanation for this appears to be the fact

that women have their disease diagnosed earlier than males, have a higher proportion of localized disease when diagnosed, and have a better survival than males in comparable stages. This difference in mortality rates does not exist over age 50.

Initial Clinical Findings

Characteristically, the patient gives a history of excellent health until the onset of his disease. This usually is manifested by adenopathy with or without systemic manifestations. Occasionally a brief antecedent history of upper respiratory infection or of infections about the head and neck is given. The duration of symptoms and of physical findings before biopsy is variable. Delay by the patient or by his physician prior to the recognition of the disease may be considerable.

The presenting symptoms most commonly are those of painless, progressive enlargement of a superficial lymph node or a group of lymph nodes, especially in the neck, and various systemic manifestations including malaise, anorexia, weight loss, nausea, vomiting, fever, or pruritus. The order of frequency of involvement of the superficial lymph nodes is the cervical, 60 to 80%, the axillary, 6 to 20%, and the inguinal, 6 to 12%. The mediastinal and/or retroperitoneal lymph nodes may be involved initially in as many as 40% of patients. The liver and the spleen are less commonly clinically involved in the early phases of the disorder.

Biopsy

Therapy for Hodgkin's disease should not be undertaken without histologic confirmation of the diagnosis. After ruling out local causes for lymph node enlargement, such as tonsilitis, infections of the hands and feet, dermatitis or pediculosis capitis, and after eliminating systemic causes, such as infectious mononucleosis, tuberculosis, syphilis, sarcoid, systemic lupus erythematosus or reactions to diphenylhydantoin and related compounds, biopsy of an enlarged lymph node should be performed. If the disease is confined to deep lymph nodes in the thoracic or retro--peritoneal regions, a scalene lymph node biopsy, thoracotomy, or laparotomy may have to be considered. Certainly, no more than 3 to 4 weeks should elapse between the recognition of an unexplained lymph node enlargement and the performance of a biopsy. It is advisable to remove large lymph nodes rather than superficial or small ones. The disease process is more likely to be evident in the former. At times, the pathologist may be unable to give a definite answer. It is a disservice to the patient to start therapy when the diagnosis is in doubt. A second biopsy of another lymph node often gives the answer. As a rule, the pathologic features are most easily recognized in biopsies from the cervical lymph node chains. Biopsy of inguinal lymph nodes is to be avoided if possible, particularly in men, because the interpretation may be made difficult by previous chronic infectious processes. If a biopsy of a femoral, iliac, or retroperitoneal lymph node is contemplated, it is advisable to perform it prior to lymphangiography as a non-specific inflammatory reaction to the Ethiodol[R] may in part obscure the histology of the lymph node.

Histologic Stages

Biopsy serves not only to arrive at a definitive pathologic diagnosis of Hodgkin's disease but allows consideration of the differences in natural history of the disease as related to its pathologic picture. The histologic classification of the lymphomata generally consists of the lymphosarcoma group subdivided as giant follicular lymphosarcoma, small cell lymphosarcoma, and larg cell lymphosarcoma, and of Hodgkin's disease generally now subdivided into the stage of lymphocytic predominance, of nodular sclerosis, of mixed cellularity, and of the lymphocytic depletion, the latter again subdivided into the stage of diffuse fibrosis and reticular type. A third histologic classification is generally reserved for malignant lymphomas which cannot be classified fully.

Clinical Stages

Hodgkin's disease is specifically staged at the time of diagnosis in order to plan the appropriate therapeutic program. The need for an acceptable staging classification for Hodgkin's disease has been emphasized at recent conferences in the United States of

America, in France, and in other countries. The current staging definitions represent modifications of the widely used classification of Peter's which divided the disease into three groups: 1) the local, which consisted of a single organ site or a single lymphatic region; 2) the regional, which consisted of two or more adjacent lymphatic lesions, or a single organ and regional lymph nodes; and 3) disseminated disease, which consisted of many groups of lymph nodes or of other organ involvement. Any of these three groups could be with or without symptoms. Kaplan proposed an additional grouping. The American Cancer Society and the National Institutes of Health in the U.S.A. have adopted a modified classification of Hodgkin's disease. In this group, Stage I-1 is lymph node involvement limited to one anatomical region. Stage I-2 is lymph node involvement limited to two contiguous anatomical regions on the **same** side of the diaphragm. Stage II is disease in more than two non-contiguous regions on the **same** side of the diaphragm. Stage III is disease on **both** sides of the diaphragm, but limited to lymph nodes, spleen, and Waldeyer's ring. Finally, Stage IV consists of those patients who have involvement of the bone marrow, lung parenchyma, pleura, liver, bone, skin, kidneys, gastrointestinal tract or any tissue or organ **other** than lymph node, spleen, or Waldeyer's ring. All stages are subclassified "A" or "B" to indicate the absence or presence, respectively, of systemic symptoms. Any of the following symptoms will be considered as significant: documented, otherwise unexplained fever, night sweats, pruritus, or weight loss of more than 10% of normal body weight. Other signs or symptoms of Hodgkin's disease are important to document but are not considered sufficient in themselves to relegate a patient to the "B" subgroup. These include malaise, weakness, fatigue, anemia, leukocytosis, leukopenia, lymphopenia, elevated sedimentation rate, cutaneous anergy, or alcohol pain.

The following studies are considered desirable for accurate staging: 1) careful history with special attention to the systemic symptoms described above; 2) complete physical examination; 3) complete blood count including a white blood cell count, differential count, hematocrit or hemoglobin, platelet count, and erythrocyte sedimentation rate; 4) "PA" and lateral chest film, whole lung tomograms in presence of hilar adenopathy; 5) skeletal survey to include at least the thoraco-lumbar spine and pelvis; 6) retroperitoneal studies to include lower extremity lymphangiography if possible and an exploratory urogram; 7) bone marrow examination with an histologic section of the marrow clot or, if possible, a needle biopsy or open marrow biopsy; 8) liver function test to include a serum alkaline phosphatase; 9) renal function tests to include a urinalysis; and 10) documentation of cutaneous anergy.

From the list above it is obvious that the clinical findings with radiologic studies is extremely important and useful. Lung tomography, intravenous pyelography, and gastrointestinal studies have been employed for many years. More recently, employment of radio-opaque iodized oil, Ethiodo-R, for lymphangiography; radioactive gold, Au^{198}, for liver scanning and bone marrow scanning; heat-damaged Cr^{51}-labeled red cells for spleen scanning; and I^{131} aggregated albumin for lung scanning has added new dimensions to the meaning and limitations of "clinical local disease".

The usefulness of the liver scan is shown on the next slide. In this particular patient, there are seen two areas in which the $gold^{198}$ has not been taken up by the Kupfer cells of the liver. At post-mortem examination, it was shown that there was a large, single metastasis in the left lobe of the liver and that, in addition, a large, bulky mass of lymphoid tissue in the porta hepatis was enlarging this particular area making the uptake appear to be decreased in the area of the porta hepatis. Liver scans are often difficult to interpret, however, in examples such as the one shown they may be extremely helpful in pointing to areas grossly involved by Hodgkin's disease. The second tchnique is the spleen scan performed with heat-damaged Cr^{51}-labeled autologous red cells. As shown in this particular slide, one can detect enlargement of a spleen which may have been missed on physical examination and on flat plate of the abdomen. Detection of isolated masses in the spleen is considerably more difficult than in the liver, and such findings must be interpreted with great caution.

Lymphangiography is probably the most useful of the techniques which were mentioned. The next slide shows an intravenous pyelogram; it can be readily seen that on the left there is displacement of the ureter in the upper one-third by a mass. In most instances, this would be sufficient to alert the clinician to the presence of retroperitoneal nodes. In this particular patient, however, it was desirable for other reasons to perform lymphangiography. The next slide indicates that the deviation of the ureter is due to an enlargement of a lymph node by involvement with Hodgkin's disease. The next slide shows the usefulness of a lymphangiogram in a patient who had established Hodgkin's disease and recurrence of symptoms including fever, weight loss, and itching. Physical examination and routine tests failed to reveal the location of the recurrent disease; however, by lymphangiography, shown on this and subsequent slides, involvement of the retroperitoneal lymph node chain by Hodgkin's disease could be readily demonstrated. The second slide in this series points out the usefulness of an oblique film and the third slide, the usefulness of a lateral film in the analysis of lymphangiographic studies.

Lymphangiography appears to be indicated in Stage I and II-A patients with disease above the diaphragm to rule out the presence of retroperitoneal involvement before administering radical radiation therapy to the diseased nodes and to the contiguous areas. If retroperitoneal disease is discovered, as it is in about 10% of cases with cervical Stage I disease and in one-third of patients with cervical Stage II-A disease, this occult disease can be treated with radiation therapy in an attempt to eradicate all known foci of disease. It is in these groups, old Stage I and old Stage II-A, in whom the most interesting observations relative to the usefulness of lymphangiography and prophylactic radiation therapy will evolve. Namely, how much does the discovery of asymptomatic retroperitoneal Hodgkin's disease and its subsequent treatment with current modes of therapy prolong survival?

Lymphangiography is usually not indicated in patients with the old Stages II-B and III disease. Ninety per cent of these patients have retroperitoneal disease. A lymphangiogram would seem necessary only if it is planned to cure patients with generalized Hodgkin's disease with irradiation of all involved lymph node-bearing areas. This program is under investigation in a number of radiotherapy centers.

The complications of lymphangiography should be kept in mind when performing these studies. They include: symptomatic pulmonary oil embolism; oil embolism to other organs, including kidney, brain, and liver; cellulitis at the site of injection; allergy to iodine-containing dye or to the blue dye used for tracing the lymphatic vessels; occasional fever lasting 12 to 36 hours after injection of the contrast material (this may be associated with excessive pulmonary oil embolism); and transient pain usually at the site of involved nodal masses within the abdomen or pelvis.

The contra-indications to this diagnostic test, therefore, are: parenchymal pulmonary disease whether it is symptomatic or not; patent foramen ovale; renal vascular disease; or other underlying conditions predisposing to excessive deposition of Ethiodol[R] in a vital organ; excessive intra-abdominal disease, especially with palpable nodal involvement below the diaphragm; and a history of allergy to the iodine-containing or blue dyes.

Whereas the staging classification just discussed is of great practical value, a number of additional factors of prognostic significance should also be considered. These might be particularly important in patients classified as Stage III or Stage IV. These factors to be discussed in greater detail in a later portion of this Symposium include the age of the patient, the sex of the patient, the duration and number of signs and symptoms, the exact location of presenting lymph nodes, and the completeness and duration of response to initial therapeutic procedures. Although these factors and the stating are of general value in predicting the clinical course, it must be remembered that there is no single, reliable prognostic sign for an individual case.

Course of Disease

The clinical course of Hodgkin's disease is characterized by great variability. Progression is by successive exacerbations which occur at intervals of weeks, months,

or years. Fever occur eventually in over 50% of cases and is cyclic, continuous, intermittent, or more rarely, the Murchison--Pell-Epstein type. The pulse is rapid. Drenching sweats are common in presence of fever but occur also in its absence. Weakness, fatigue, weight loss, and cachexia eventually occur in all patients. Up to 85% of the cases have pruritus at some time.

Intrathoracic involvement is frequent. In a study of 50 cases coming to post--mortem examination, the centrally located lymph nodes (the mediastinal and hilar lymph nodes) were involved in 49 out of 50 cases. The involvement of other structures was also frequent, particularly the lungs, the bony thorax, and the pleura. In addition, the diaphragm, the heart, the pericardium, the thymus, and the esophagus may be involved. Pulmonary involvement may appear in 15 to 50% of cases. Hodgkin's disease may be primary in the lung, but more often there are direct infiltrations from the mediastinum or multicentric lesions, originating presumably by hematogenous spread. A few patients are asymptomatic; the majority complain of dry, hacking cough, chest pain, and of those signs and symptoms which are commonly associated with active Hodgkin's disease. In addition, a few have hemoptysis, dyspnea, and the signs of pneumonitis. The involvement of the pulmonary area may be subpleural, bronchial, or endobronchial, the latter often leading to atelectasis, parenchymal which may be isolated or massive and occasionally may terminate in cavitary lesions, and non-specific, including fibrosis. Most frequetly the lesions are located in the upper lobes.

The next slide shows the chest film of a patient who has a cavitary lesion, proven at autopsy to be due to Hodgkin's disease alone. The next slide shows an even more complex picture of a patient with Hodgkin's disease treated eight years earlier with extensive radiotherapy who, at the time this radiologic examination was done, had pulmonary fibrosis secondary to the radiation. In addition, he had infiltrations due to Hodgkin's disease and one of these, in the right middle lobe, had a cavity. In addition to these lesions, one may encounter pleural effusions; radiation fibrosis and penumonia; pneumonitis due to bacterial and fungal infections; and pulmonary edema due to congestive heart failure secondary to anemia. Pulmonary fibrosis with severe restriction of ventriculatory capacity may appear in the course of the disease or as a result of radiotherapy to the lung. The next slide shows a patient who had **no** intrathoracic disease and had a normal maximal breathing capacity before radiation therapy to her breast, axilla, and internal mammary chain for cancer. Two hundred days following her radiation treatment, her maximum breathing capacity was severely diminished and, as shown on the next slide, the work of breathing was markedly increased, that is, a greater pressure was necessary to inhale a given volume of air folowing therapy than during the control period. It is believed that these changes are due to the fact that radiation makes the expansion of the thoracic cage more difficult and stiffens the underlying pulmonary tissue.

Abdominal and retroperitoneal involvement is extremely frequent in the course of Hodgkin's disease. The gastrointestinal tract appears to be involved in about 15% of patients coming to autopsy. Most frequently the disease occurs in the stomach and in the small bowel. The symptoms are due to infiltration of the gastrointestinal tract, or due to pressure from large retroperitoneal masses, or from enlargement from the spleen and liver. The spleen, initially affected in up to 30% of patients, eventually is involved in 80% of cases. In the presence of enlargement of spleen, hypersplenism may occur; this will be discussed later.

Hepatomegaly is an early finding in about one-third of cases. Liver involvement, determined microscopically, occurs in over half of patients. However, in two large series the incidence of clinical jaundice was only 10 to 15%. In addition, in a series of 101 patients with jaundice and proven Hodgkin's disease accumulated at the Memorial Hospital, involvement of the liver with Hodgkin's disease occurred in only 16% of the cases. Other liver disease accounted for the jaundice in these patients, including serum hepatitis, toxic hepatitis, cholelithiasis, passive congestion, viral hepatitis, a liver carcinoma, and in 49% other

causes which could not be clearly delineated. The pathologic findings in the liver of 15 jaundiced patients with Hodgkin's disease who did not have tumor involvement in the liver or extrahepatic bile ducts revealed that the majority had passive congestion or fatty metamorphosis and others, hemosiderosis and non-specific atrophy of the liver cells. Various types of extrahepatic bile duct involvement were seen in 14 jaundiced patients with Hodgkin's disease and included pressure on the common duct by lymph nodes, infiltration of the common duct, and occasionally pressure on the hepatic duct.

Bone involvement as manifested by pain, radiologic evidence of destruction, or frank fractures are found in 15 to 30% of cases. The thoracolumbar vertebrae are most frequently involved; the pelvis and sacrum less frequently; the ribs, sternum, and skull the least. One-third of the lesions appear to be sclerotic; less than one-third, lytic; and the remainder, mixed. Hypercalcemia occurs in 10 to 20% of cases; usually, hypophosphatemia is also present and the serum alkaline phosphatase is elevated. Radiologic examination may be negative for bone involvement but bone involvement appears to occur in 60% of patients coming to autopsy and having a thorough study of the skeletal system. However, there are occasional cases in whom hypercalcemia may occur without any bone involvement by Hodgkin's disease.

Abnormalities of the central nervous system are noted in over 10% of patients. The brain or spinal cord may be invaded directly; however, more commonly, symptoms are due to compression of the spinal cord. Peripheral neuropathy and cranial nerve palsies may occur. Toxic encephalitis, without manifest lesions of Hodgkin's disease in the brain, particularly involving the cerebellum (cerebellar leukoencephalopathy) has been reported. Alcohol intolerance has been described in 17 to 20% of cases but does not appear to be specific for Hodgkin's disease. The most important neurologic complication of Hodgkin's disease is cord compression occurring in approximately 25% of patients who have some neurologic abnormality. It is characterized by weakness, paresthesias, back pain, and leg pain, and, in later stages, by difficulties with urinary and bowel control. The thoracic spine appears to be involved in 62% of cases; the lumbar spine in 24%. Physical examination may reveal abnormalities suggesting cord involvement. Radiologic examination of the spine and particularly myelography may more accurately localize the lesion. This complication constitutes a medical emergency and decompression by neurosurgery, nitrogen mustard treatment followed by radiotherapy, or radiotherapy alone or after surgical decompression, is the treatment of choice. Herpes zoster will be discussed in conjunction with the other infections encountered in Hodgkin's disease.

Skin involvement may be due to direct invasion by Hodgkin's disease, an "id" reaction, or excoriations produced in response to pruritus. Almost any other organ may be involved initially or in late stages by Hodgkin's disease. Thus, reports of Hodgkin's disease of the thyroid, breast, ovary, cervix, vulva, bladder and other genitourinary areas, nasopharyns, and the larynx have appeared in the literature.

Most studies indicate that pregnancy can be well tolerated particularly in patients who have the chronic form of the disease. It has been suggested that pregnancy should be avoided until 2 to 5 symptom--free years have passed.

Laboratory Findings

Anemia may occur with localized disease but it is almost uniformly present in the late stages of Hodgkin's disease. Except for a few cases of hypochromic anemia, secondary to blood loss, the majority of patients have normochromic, normocytic anemia. The direct Coombs test is usually negative. The next slide summarizes the results of a red cell life span study in a patient with severe anemia and splenic enlargement. A marked decreased in the Cr^{51} red blood cell life span and significant sequestration of red blood cells in the spleen are seen. Klein and Berlin and others have reported similar findings. In addition, hypoferremia and abnormalities in iron metabolism, as measure by Fe^{59}, and consisting of excess uptake of iron by liver and spleen, impaired incorporation of iron into erythrocytes, and for re-utilization of hemoglobin iron have been noted. The anemia becomes progressively worse as the disease advances and

correlation with disease activty is often possible.

The changes in the white blood cells are not constant and not diagnostic. Leukocytosis with neutrophilia is often present. Monocytosis or lymphocytosis occurs occasionally early in the disease. Leukopenia and, in particular, lymphopenia are seen in advanced disease and will be discussed later in this Symposium. Eosinophilia is frequently found and occasionally may be marked. The platelets are normal or increased in the beginning of the illness, but usually diminished in the course of the disease. The leukocyte alkaline phosphatase value is often elevated during the active phases of the disease and falls during remissions. In about 5% of cases of Hodgkin's disease, myeloid metaplasia associated with hypoplastic marrow or tumor infiltration of bone marrow may be seen. Bone marrow aspiration is usually not helpful in ruling out bone marrow involvement, and formal biopsy may be necessary. When present, Reed-Sternberg cells are readily recognizable. On very rare occasions these cells have been found in the blood. The erythrocyte sedimentation rate is elevated in the presence of active disease and falls after effective therapy or during spontaneous remission.

Hypercalcemia may occur and is usually associated with hypophosphatemia and elevated serum alkaline phosphatase. As already mentioned, roentgnographic evidence of skeletal involvement by tumor may be absent although autopsy usually reveals osseous involvement. Hyperglycemia may be seen in association with steroid therapy or during exacerbations of the disease. Gout and decreased renal function following persistent hyperuricemia have been reported. Uremia may occur as a terminal event. Serum abnormalities occur regularly. Albumin is often reduced, mainly due to a decrease in synthesis. Alpha-1, alpha-2, and beta-2 globulins are usually increased; the alpha-2 globulin may be increased in up to 77% of the cases. The increase in the alpha-2 globulins is largely due to an increase in haptaglobin and ceruloplasmin. An increase in hexose bound to alpha-2 globulin has been noted by Whitmore in lymphomata including Hodgkin's disease. Although some authors feel that hypogammaglobulinemia is seen only rarely in patients with Hodgkin's disease, we have found that significant hypogammaglobulinemia (i.e., less than 0.9 gm% gamma globulin) occurs in almost half (48%) of the cases, particularly in advanced disease.

Complications and Cause of Death

The clinical condition or conditions apparently responsible for the patient's death in 115 cases studied at our hospital included: severe infection, failure of pulmonary function, central nervous system involvement or malfunction, gastrointestinal bleeding, and liver failure. In 30 patients, anemia, leukopenia, thrombocytopenia, or a combination of these, mainly attributable to antecedent therapy contributed to the death of the patient.

The frequency of infections merits further examination. A number of investigators have described the characteristics of the immune defect found in Hodgkin's disease. As Aisenberg will summarize later, anergy to tuberculin, tricophiton, candida, streptokinase, and diphtheria toxin as well as delayed homograft rejection have been demonstrated in some of the patients with Hodgkin's disease. Response to vaccination with typhoid, mumps, pneumococcal polysaccharides, and other antingens has been inconcluisve. Properidin levels are low; serum complement normal. Cellular defense mechanisms measured by skin-window technique appear to be normal. Lymphopenia and low gamma globulin levels have already been mentioned.

The next slide summarizes the various types of infections which were encountered at the National Institutes of Health in Bethesda, Maryland, by Carbone **et al.** Of 86 patients, 36 had bacterial infections, 17 viral infections, 10 fungal infection, and 3 miscellaneous infection. The number of episodes of infection per patient was 1.7; the number of episodes of infection per patient with infection was actually 2.3. As regards the bacterial infections in the U. S. National Institutes of Health series, 36 cases were encountered: 29 with septicemia, 14 with pneumonia, and 13 with enteritis, urinary tract, skin infections, and miscellaneous infections. Common organisms observed were **Staphylococcus aureus, Escherichia coli,** and **Pneumococcus pneumonii. Salmonella typhimurium** and **Kleb-**

siella pneumoniae were also encountered. **Pneumocystis carinii, Listeria monocytogenes,** and others have been reported. In our own series, we have examined the frequency, distribution, and types of bacterial infection in 141 patients with Hodgkin's disease seen between 1951 and 1965. We were able to demonstrate that leukopenia and neutropenia predispose only rarely to bacterial infection; that lymphopenia and hypogammaglobulinemia progress as the disease advances; and that this appears to predispose patients to infections. Antecedent radio—or chemotherapy and corticosteroids may increase further the risk of infection. The fact that the 5-year survival probability for the entire group, for the patients with bacterial infections, and for those without bacterial infections was the same, 27.4%, permitted analysis of our data by quarters, i.e., dividing the course of each patient living more than six months into four equal parts. Fifty-four patients had 82 episodes of bacterial infection; 17 patients had 19 episodes of herpes zoster; and 16 patients had severe fungus infection, mainly moniliasis. Although some of the infection occurred in the first, second, and third quarters, the majority of infections and the majority of recurrences of infections occurred in the fourth quarter of the patient's illness. Some of the patients were afflicted not only with bacterial infections but had concurrent infections with herpes zoster and superinfections with monilia.

Neither the leukocyte count nor the absolute neutrophilic granulocyte count appeared to correlate with the incidence of infections. The data for the neutrophilia actually emphasize the point that particularly in the first three quarters it was more often due to the underlying Hodgkin's disease than to bacterial infections. The findings regarding the absolute lymphocyte count in patients with and without bacterial infection have been analyzed. The normal lymphocyte level ranges from 1500 to 3000 per cubic mm. There appears to be a progressive, statistically singnificant. fall in the lymphocyte count in all the patients as the disease advances. By the fourth quarter, 111 out of 126, or 88% of patients, had lymphopenia. This supports data previously published by Aisenberg and by others. Whereas in the first 3 quarters, only 10 of 18 (56%) patients with infection had lymphopenia, in the final quarter, 37 of 44 (34%) patients with infection had lymphopenia. The risk for a patient with lymphopenia of developing bacterial infection in the fourth quarter is 33% (37 out of 111). The serum gamma globulin level, plotted in grams per cent, in patients with and without infection was also examined. In the third and fourth quarters there was a significant decrease in the mean gamma globulin level compared to the first two quarters. In the fourth quarter, 31 out of 84 patients (37%) had a gamma globulin below 0.95 gram%. The risk for a hypogammaglobulinemic patient developing a bacterial infection in the fourth quarter is 54% (17 out of 31).

The occurrence of bacterial infections following administration of radiotherapy, chemotherapy, or corticosteroids was examined next. Of the 141 patients, the 87 who never developed infection had 130 courses of radiotherapy, 156 courses of chemotherapy, and 50 courses of corticosteroids. The 54 cases with eventual bacterial infections also had many courses of radiotherapy (97), chemotherapy (60), or steroids (15) with no subsequent infection. Especially in the fourth quarter, however, this group of patients experienced bacterial infections often related to antecedent chemotherapy (41) or treatment with corticosteroids (25). The risk of bacterial infection following therapy increased greatly from the first three quarters to the fourth quarter. Thus, following radiotherapy, it increased from 0.5 to 19%, following chemotherapy from 5 to 34%, and following steroids from 4 to 38%.

Regarding the therapy of bacterial infections, none of the patients was on prophylactic antibiotics or gamma globulin; each infection was treated with appropriate local measures where applicable and with specific antibiotics as determined from sensitivity studies on the isolated bacteria.

The clinical importance of these bacterial infections is emphasized by the following findings. In 26 of the 54 patients, meningitis, septicemia, pneumonia, severe urinary tract infection, or a combination of these, contributed to the death of the patient; however, all patients died with

active Hodgkin's disease and none from infection alone. These data appear to indicate that leukopenia and granulocytopenia are not important in determining the occurrence of bacterial infections in patients with Hodgkin's disease. The presence of lymphopenia occurring in 88% and of hypogammaglobulinemia in 37% of cases in the fourth quarter predisposes a significant number of individuals to infection. The administration of radiotherapy and, particularly, of chemotherapy and steroids aggravates the tendency to contract bacterial infections.

There were several patients with severe monilial infection; two-thirds of these had hypogammaglobulinemia. Some patients had central nervous system tolurosis. Other types of fungi, including aspergillosis, mucormycosis, and nocardiosis have been encountered.

The occurrence of viral infections has been documented in a number of series. At the U. S. National Institute of Health, herpes zoster, varicella, cytomegallovirus, and herpes simplex have been described. In our own series, 17 patients had 19 episodes of herpes zoster. Generalized zoster occurred in six cases. Hypogammaglobulinemia was present in 8 of 10 cases, and leukopenia in 6 of 19. In 9 of the 19 episodes, chemotherapy proceded the appearance of the herpes zoster. During steroid administration, 6 patients developed herpes zoster and 4 of these had generalized herpes zoster involvement.

Unquestionably, infections contribute in a major way to morbidity and mortality in Hodgkin's disease. In many instances the patients were already in the advanced phase of their disease when they contracted their infection. It is difficult to assign responsibility to the various factors involved in the high rate of infection. They include: 1) deficit in antibody formation, hypogammaglobulinemia, and lymphopenia; 2) failure of cell-bound antibody mechanisms; 3) possibly leukopenia and neutropenia secondary to replacement of bone marrow, hypersplenism, and drug or radiation toxicity; 4) glucocorticoid administration; 5) prior administration of antibiotics; 6) debility and poor nutritional state; and, finally, 7) local predisposing factors such as tumor involvement or radiotherapy.

Others in this Symposium will discuss in detail the immunologic aspects, staging and prognosis, pathologic features, radiotherapy, and chemotherapy of Hodgkin's disease. Knowledge of the natural history of Hodgkin's disease, of the complications which might be expected, and of the therapeutic modalities available helps the physician plan for the total care of the patient.

IMMUNOLOGIC ASPECTS OF HODGKIN'S DISEASE*

DR. ALAN C. AISENBERG

1. Introduction

This presentation is concerned with the immunological deficiency of Hodgkin's disease, a deficiency which contributes to the infectious complications seen so frequently in this disorder. The defect also raises important questions about the pathogenesis of Hodgkin's disease.

A high incidence of tuberculosis in patients with Hodgkin's disease led Ewing (19) to comment that "...tuberculosis follows Hodgkin's disease like a shadow." Jackson and Parker (34) reported coexistent tuberculosis in 20 per cent of their cases and more recently, it has been noted that Hodgkin's patients have a proclivity to a variety of fungal infections as well, particularly cryptococcosis. Although this predisposition to certain infectious complications, of itself, raised the question of an immunological deficiency in Hodgkin's disease (18), it was through tuberculin testing of Hodgkin's patients that the immune defect was demonstrated.

In the 1930's several investigators (Steiner (68) and Parker **et al.** (53)) noted that the percentage of positive tuberculin reactions obtained in Hodgkin's disease patient was much lower than that found in a comparable control population. Most remarkable, however, was the observation that in Hodgkin's disease the tuberculin reaction frequently remained positive in the face of overt tuberculosis. Finally, in the 1950's, with the increased understanding of cellular immunity then available, Schier and his colleagues (61, 62) were able to show that the depressed reactivity of the Hodgkin's patient to tuberculin was but one manifestation of impaired delayed hypersensitivity.

2. Depressed Delayed Hypersensitivity — Loss of Preexisting Allergy

Immunological reactivity can be divided into the immediate type mediated by antibody and the delayed type mediated by cells. Delayed hypersensitivity is best studied by skin testing, and the slow evolution of the skin reaction over 48 hours and longer after application of the allergen differentiates this type of immunity from the immediate Arthus skin reaction. Tuberculin hypersensitivity and contact allergy are two classical examples of delayed hypersensitivity. Depression of this form of immunolo-

* The author's work is supported by Research Grant No. CA-07179 of the National Cancer Institute, United States Public Health Service.

gical response is called "anergy" and is the predominant immune deficiency of early, active Hodgkin's disease.

Schier **et al.** (61, 62) tested a group of Hodgkin's patients and normal controls with four delayed-type allergens (mumps skin test antigen, **Candida albicans, Trichophyton gypseum** and purified tuberculoprotein) and found that 68 to 92 per cent of the controls reacted to the various antigens but only 14 to 23 per cent of the Hodgkin's group responded (Table I). This unreactivity to delayed allergens has been amply confirmed (38, 68).

It is important to point out that the anergy of Hodgkin's disease differs significantly from the anergy which may accompany advanced cancer and other debilitating illnesses. This is illustrated in Table II from the work of Lamb **et al.** (38) in which anergy is defined as unreactivity to all six of the following allergens: mumps skin test antigen, diptheria toxoid, **Candida albicans, Trichophyton gypseum,** streptokinase-streptodornase, and purified tuberculoprotein. This table clearly indicates that while cancer, leukemia and non-Hodgkin's lymphoma patients are frequently anergic when in poor clinical condition, only Hodgkin's patients are anergic when their clinical status is **good.**

3. Depressed Delayed Hypersensitivity — Active Sensitization

Determination of anergy by testing for previously acquired sensitivity has the disadvantage that the anergic patient cannot be distinguished from the individual never exposed to the allergen. This difficulty can be overcome by assessing the ability of the individual to acquire sensitivity to a material of such unusual character that absence of exposure can be assumed, or to a material to which preexisting sensitivity can be ruled out by skin test. It should be pointed out that the ability to acquire sensitivity is probably a more demanding criterion of normal cellular immune function than the ability to maintain preexisting hypersensitivity.

The technique which has been used most extensively to assess delayed hypersensitivity in Hodgkin's disease is sensitization to the contact allergen dinitrochlorobenzene (37). Two to four weeks after the application of a concentrated (usually 10 per cent) acetone solution of dinitrochlorobenzene, the subject is tested by the application of a dilute solution (0.1 per cent), a concentration to which an unsensitized individual will not respond. The initial application sensitizes at least 95 per cent of young, healthy controls (31, 37), but none of a group of 25 individuals with active Hodgkin's disease (1) could be sensitized (Table III). However, some Hodgkin's patients with inactive disease, including all those whose disease was inactive for periods greater than two years, could acquire dinitrochlorobenzene sensitivity. In this study two patients were of particular interest; anergic with active disease when first studied, these individuals recovered normal skin reactivity after a prolonged irradiation-induced remission. It should be emphasized that a number of the anergic Hodgkin's individuals in this study had early disease which by clinical criteria was quite localized. A second group of workers has confirmed the inability of the Hodgkin's patient to develop contact sensitivity, but the less uniform sensitization of normal controls observed may have been the result of differences in the technique of sensitization (41). Depression of the delayed hypersensitivity response to dinitrochlorobenzene has also been observed in patients with chronic lymphatic leukemia (16), malignant epithelial neoplasms and chronic non-neoplastic disease (31).

Kelly **et al.** have attempted to induce delayed hypersensitivity in Hodgkin's patients with diptheria toxoid (36). Whereas 9 of 14 controls were sensitized by the procedure they employed, the 9 Hodgkin's patients could not be sensitized. Sokal and Primikirios, however, were able to convert 10 of 12 patients whose Hodgkin's disease was free of systemic manifestations to tuberculin positive status with BCG, but could not convert 3 individuals with such manifestations (66). It is possible that the discrepant results with contact sensitization and with BCG reflect differing strengths of the antigenic stimulus, or that BCG may be actually functioning as a secondary antigenic stimulus in some Hodgkin's patients. It should be noted that two patients were

observed to recover tuberculin sensitivity following the remission of their disease, while two additional patients became tuberculin negative when the conditions exacerbated (66). Recovery of tuberculin sensitivity associated with the remission of Hodgkin's disease has been commented upon in the past (14, 18).

4. Antibody Formation

The adequacy of antibody formation in Hodgkin's disease has been the subject of some debate. While certain investigators have reported depressed antibody response to pneumococcal polysaccharide (21, 39), brucella (18) and primary immunization with tetanus toxoid (9), essentially normal antibody response to typhoid-paratyphoid (33, 36), mumps (62), tularemia (60) and secondary tetanus immunization (9) have been observed by others. Normal levels of isohemagglutinins (20) and complement-fixing antibodies to a variety of common viruses (51) have also been noted. Despite these discordant findings there can be little doubt that the anergic Hodgkin's patient is able to form normal amounts of antibody in response to some antigenic stimuli. Thus, it was recently observed that normal amounts of antibody to both Types II and VII VII pneumococcal polysaccharide were produced in 13 of 19 individuals with this disorder (6). Four of the six who failed to produce normal amounts of the two antibodies were in very poor general condition and died within 6 months of completion of the immunological studies.

Thus antibody formation appears to be largely intact except in the final months of Hodgkin's disease, though there are suggestions that a subtle deficiency in this function may exist. For example, antibody synthesis may not be sustained in the normal manner in Hodgkin's disease (4, 33), and there may be depression of the primary as opposed to the secondary antibody response (9). These matters require further investigation, particularly with respect to the transition from macroglobulin to 7S-antibody synthesis.

Immunoglobulin levels (IgG, IgM, and IgA) are within normal limits in Hodgkin's disease (8, 46), a finding consistent with the preservation of antibody function. However, it is generally conceded that gamma globulin levels may decline in the terminal stage (70).

5. Homograft Reaction

The homograft reaction is probably a more complex immunological function than either delayed hypersensitivity or antibody formation (12). At present, it is believed that homografts are rejected in most instances by a cellular mechanism similar to the one involved in delayed hypersensitivity but that exceptionally, rejection may be mediated by antibody. In Hodgkin's patients, 17 (59 per cent) of 29 experimental skin grafts persisted for 30 days or longer)30, 36, 48). However, such abnormal survivals were also observed in 10 of 23 individuals with chronic lymphatic leukemia and multiple myeloma, two diseases in which humoral rather than cellular immunity is depressed (26, 47, 71). The protracted graft survivals in these latter diseases make it difficult to use homograft survival in Hodgkin's patients to incriminate a cellular immune defect. A single Hodgkin's individual has been reported in whom there was protracted survival of a bone marrow graft resulting in a chimeric state (10).

6. The Lymphocyte in Hodgkin's Disease

During the past two decades experimental evidence coming from a variety of sources has made it clear that lymphoid cells are important mediators of immunological reactivity, particularly cellular immunity (28, 42). Thus the depression of cell-mediated, delayed hypersensitivity in Hodgkin's disease calls attention to the lymphocyte in this disorder.

The medical literature prior to the Second World War is replete with observations of lymphocytopenia in Hodgkin's disease. Wiseman (74), for example, reported that 27 of 31 individuals with this disorder had depressed lymphocyte counts, and Rosenthal in 1936 (58) stressed the importance of tissue lymphocyte depletion in prognosis. When this problem was reinvestigated recently, it was readily confirmed that profound lymphocytopenia was a regular feature of advanced Hodgkin's disease (4). At the onset of the disease, however, at a time when the patient may be anergic,

blood lymphocyte counts were only slightly depressed or in the low normal range. It is thus hard to account for the anergy of early Hodgkin's disease in terms of lymphocytopenia.

Since lymphocytes may not be lacking in number in early Hodgkin's disease, is is reasonable to inquire into their function. Unfortunately, at the present time techniques for the study of human lymphocytes are just being developed, and the following conclusions must be considered tentative. Two such techniques have been employed, the measurement of lymphocyte reactivity **in vitro** and the lymphocyte transfer reaction.

Several reports suggest impaired response of cultured Hodgkin's lymphocytes. In an early study (5), 6 of 10 Hodgkin's lymphocyte samples displayed impaired response to the mitogen phytohemagglutinin and to mixed-cell culture, two conditions which regularly stimulate normal lymphocytes. In a later report, Hersh and Oppenheim (32) observed that 87 per cent of the 23 Hodgkin's patients studied showed diminution in their lymphocyte response to **in vitro** stimulation with phytohemagglutinin and vaccinia. The phytohemagglutinin-stimulated Hodgkin's cultures contained a median of 11 per cent transformed cells as compared to 70 per cent in stimulated cultures of normal controls, and vaccinia-stimulated Hodgkin's cultures showed 0 per cent transformation as compared to 8 per cent in controls. It also has been observed that the phytohemagglutinin-induced cytotoxicity of Hodgkin's lymphocytes against cultured human liver target cells is impaired (33a).

A second approach to the Hodgkin's lymphocyte is the study of the skin reaction which follows transfer of purified lymphocytes from patients with this disorder to the skin of another individual. The reaction is a complex one into which histocompatibility difference of graft and host, immunological competence and non-immunological factors may enter (29). Transferred Hodgkin's lymphocytes displayed several abnormalities which can be appreciated in Table IV; that thought to correlate best with the anergy of the lymphocyte donor was the absence of reaction of Hodgkin's lymphocytes 7 days after their transfer, a time when most normal lymphocytes still displayed a reaction. A second abnormality was seen in the Hodgkin's patients in poor condition who served as lymphocyte recipients and who were unable to support the initial reaction (48 hours) of cells transferred from normal controls. Finally, an abnormally protracted reaction (beyond 14 days) or normal lymphocytes seen in some debilitated Hodgkin's recipients was attributed to delayed rejection of the lymphocyte graft. The lymphocyte transfer reaction is of sufficient complexity that these interpretations will remain in doubt for some time to come, but the data is consistent with a functional defect of the Hodgkin's lymphocyte.

7. The Eosinophil

While the eosinophil is believed to participate in allergic reactions, particularly those mediated by reaginic antibody, the precise function of the cell remains unclear (59). It appears either to be linked to the antigen-antibody interaction, perhaps via a soluble intermediate, or to be involved in the processing of antigen or the synthesis of antibody. The presence of the eosinophil in the lesion of Hodgkin's granuloma has been repeatedly commented upon (34, 74), and eosinophilia is seen in a fraction of cases (32 per cent of Wiseman's series (74)). In view of the present uncertainty about eosinophil function, it is difficult to speculate profitably about the significance of this cell in Hodgkin's disease.

8. Infectious Complications

Tuberculosis was the first infectious complication noted in Hodgkin's patients, but with the control of the infection in the general population this complication is seen much less frequently. In its place a striking association of Hodgkin's disease with cryptococcosis and other uncommon fungus diseases has emerged. Thus 8 per cent (22), 18 per cent (15) and 5 per cent (75) of reported cases of cryptococcosis occur in Hodgkin's patients, and a similar disproportionate incidence of infection with **Nocardia, Candida, Histoplasma, Aspergillus and Actinomycetes** is seen in this condition (13). The high incidence of herpes zoster in Hodg-

kin's disease is well known (57, 73), but only recently cytomegalovirus infection has been recognized (13). It has also become clear that the incidence of **Toxoplasma** and **Pneumocystis** infection is unusually high in Hodgkin's disease (13). The observation has been made that the course of cryptococcal infection is particularly virulent in the lymphoma patient (13).

While fungi, and certain viruses and protozoa are the **characteristic** microbial agents in the Hodgkin's patient, bacterial infections remain the most **common** infectious complications of the disorder. The spectrum of such complications in a carefully studied group of 51 Hodgkin's patients was presented is presented in Table V (13). Of 86 episodes **cles to the Control of Hodgkin's Disease,** and cent Rye, New York **Conference on Obsta**by Casazza, Duvall and Carbone at the reof infection, 56 were of bacterial etiology either alone or in combination with other agents. The bacterial invaders are those which are prominent in hospital medicine: **Staphylococcus aureus, Pseudomonas,** and **E. coli.**

It hardly requires reiteration that resistance to infection is a complex phenomenon dependent on the integrity of the skin and mucous membranes, phagocytosis by granulocytes and the reticuloendothelial system, non-specific humoral factors including interferon (virus infection), and finally the specific cellular and humoral immunologic mechanisms. Since the importance of each component is different for each microbial agent, it is unlikely that a single explanation will account for the varied infectious complications of Hodgkin's disease. Howver, it does contributes significantly to the susceptibility of these individuals to fungal and other infections, particularly when it is noted that delayed hypersensitivity has always been considered critical in resistance to tuberculosis and fungal infections. It appears that a high degree of anergy is needed, since clinical infection is ordinarily seen only late in Hodgkin's disease (13, 65). Presumably, the susceptibility to bacterial infection reflects depression of both cellular and humoral immunity in the far advanced Hodgkin's patient, as well as loss of continuity of the skin or mucous membranes due to local factors. The part played by corticosteroids and chemotherapeutic agents (known to be immunosuppressive) in all these infections is difficult to assess.

9. Comparison of the Immune Defects of Hodgkin's Disease and Lymphatic Leukemia and Myeloma

In considering the immunological deficiency of Hodgkin's disease it is important to separate this disease from other lymphoid disorders, particularly chronic lymphatic leukemia and multiple myeloma. The deficiency of these other lymphoid disorders differs from that under consideration in this chapter. Indeed, the defect of lymphatic leukemia and myeloma is quite similar to that of the more common, congenital, sex-linked form of agammaglobulinemia (24, 26), being characterized by hypogammaglobulinemia, poor antibody formation in the face of relatively intact delayed hypersensitivity (dinitrofluorobenzene sensitization is impaired in chronic lymphatic leukemia (16), and frequent bacterial but **not** fungal infections (47, 71). Furthermore, infections tend to punctuate the entire clinical course of these hypogammaglobulinemic states, but in Hodgkin's disease occur predominantly in the far-advanced and terminal patient (13). In addition, the pneumococcus which is such a common offender in lymphatic leukemia and myeloma only rarely attacks the Hodgkin's patient (13).

10. Progression of the Immunologic Defect in Hodgkin's Disease

It should be pointed out that Hodgkin's disease is a clinical condition with varying involvement of the reticuloendothelial system rather than an immunological entity. Presumably, the immunological defect alters and progresses with the advancing disease process. Thus, Table VI attempts to define the immunological deficiency in relation to the disease involvement. In this table, Hodgkin's disease has been divided arbitrarily into 4 divisions: 1) healed localized disease, 2) active localized disease (Stage I and II of Peters and Middlemess (56) and 3) generalized disease, progressing to 4) the terminal condition.

The immunological deficiency of early, active (localized) disease is characterized by

loss of reactivity to delayed allergens and inability to acquire contact sensitivity. Antibody function is essentially intact and the blood lymphocyte level either normal or but slightly depressed; impaired function of this cell may be reflected in the depressed reaction of transferred Hodgkin's lymphocytes. If through treatment or otherwise, a prolonged period of disease inactivity (healing) occurs, the evidence suggests that normal delayed hypersensitivity is restored.

In the progression to advanced (generalized) disease, it is likely that the depression of delayed hypersensitivity becomes more profound, though investigation of this point is elusive because of the difficulty in quantitating delayed hypersentivity. Since the ability to acquire dinitrochlorobenzene sensitivity is absent in the early patient, contact sensitization is not helpful in determining the intensity of unresponsiveness. However, there does appear to be a higher incidence of unresponsiveness to delayed allergens (38, 65, 66) in advanced Hodgkin's disease, and it is in these patients that mycotic infections appear. While gross antibody synthesis is still intact in such individuals, there are less obvious hints of disturbed antibody formation.

Although the immunological deficit is more severe in the terminal Hodgkin's patient, it is probably the least interesting because it is the least specific. In addition to depressed delayed hypersensitivity, such individuals may display hypogammaglobulinemia and poor antibody formation and with a variety of bacterial, viral and fungal agents. Such terminal patients have a complex immunological defect to which therapy greatly increased susceptibility to infection and debility undoubtedly contribute, and it is not unlikely that this terminal state shares common and nonspecific features with that of terminal carcinoma (40).

It should be emphasized that the formulation of Table VI is only an attempt at formalization. The very division of a continuous spectrum of disease into four separate categories is an approximation.

11. Nature of the Immunological Deficiency and the Relatioship to Hodgkin's Disease

There are several features which suggest a peripheral failure of the effector lymphoid cell in Hodgkin's disease rather than a central failure (immunological tolerance). Depression of delayed hypersensitivity in the face of essentially normal antibody formation and recovered of skin allergy during disease remission (without further antigen exposure) imply an intact central mechanism. The abnormalities of Hodgkin's lymphocytes **in vitro** and after transfer studies support this contention. (The failure of Lamb **et al.** (38) to transfer delayed hypersensitivity with peripheral lymphoid cells from hypersensitive normals to anergic Hodgkin's patients does not settle this pont). In late Hodgkin's disease the severe depletion of blood and tissue lymphocytes probably contributes to the complex immunological abnormalities observed. However, in the early case where the disease process is quite localized and lymphocytopenia the exception, the defect in peripheral lymphoid cells must be qualitative rather than quantitative.

It remains completely unclear how the immunological deficiency is related to the pathogenesis of Hodgkin's disease. The finding that anergy may accompany localized disease and may disappear following local treatment appears to rule out obliteration of the lymphoid apparatus as the cause of the defect. Perhaps the most reasonable sequence is that the unknown etiologic agent in Hodgkin's disease causes the anergy as well as the tissue changes that we recognize as Hodgkin's granuloma, or that the agent leads to the tissue changes which in turn cause the anergy. An alternative which, though less likely, is difficult to rule out, is that the anergy is the initial happening and leads to the specific tissue alterations.

Chase (14) has made the plausible suggestion that the anergy of Hodgkin's disease results from depression of cellular immunity by a circulating (non-cellular) factor. However, since the evidence suggests that cultured Hodgkin's lymphocytes continue to function abnormally when Hodgkin's serum is replaced by normal serum (5, 32, 33[a]), this humoral factor must do more than temporarily depress the activity of otherwise normal lymphocytes. It could be postulated that such a circulating factor, when present during the period of lymphocyte development, would result in an immunological in-

competent cell. (The observation that herpes zoster develops in anatomic proximity to active Hodgkin's tissue (73) could be taken as evidence for the production of a humoral factor with consequent local breakdown of cellular immunity).

The evidence that hypersensitivity to tuberculin is depressed during the acute stage of measles and other virus infections (52) should be mentioned. Indeed, it has recently been shown that the tuberculin reaction frequently becomes negative during the incubation period of measles, is uniformly negative during the first 4 days of the rash, and is often depressed even after vaccination with live-virus vaccine (67). Thus a viral etiology of Hodgkin's disease (which has been suspected for other reasons (2) would account for the observed anergy. However, unlike Hodgkin's disease where anergy may accompany a localized process, in measles the pathologic involvement is severe and generalized. The anergy of sarcoid also differs from that of Hodgkin's disease in that the granulomatous process is generalized and differs in other details as well (14, 26).

12. Hodgkin's Disease, Graft-Versus-Host Reactions and the Thymus

Graft-versus-host reactions are seen in experimental animals in a variety of situations where immunologically competent, genetically foreign, lymphoid cells are transferred to a host unable to reject the lymphoid graft (64). Among the frequently observed features of these reactions are lymphadenopathy, **splenomegaly,** leukocytosis, skin lesions, diarrhea, anemia (which may be hemolytic), thrombocytopenia, wasting, runting in the newborn, and death (11, 64). Kaplan and Smithers (35) have pointed out similarities between graft-versus-host reactions and malignant lymphoma; Green **et al.** (30) have raised the question of whether the patient with Hodgkin's disease could be a maternal-fetal lymphoid chimera; and Schwartz and Beldotti have reported malignant lymphoma in mice subject to graft-versus-host reactions (63). While the above reactions have obvious similarities to Hodgkin's disease, at the present time the evidence is not compelling that they play a role in the pathogenesis of the human disorder (44). Graft-versus-host reactions lack several important features of Hodgkin's disease; localized adenopathy, the infection-like picture with chills and fever of the disseminated process, and the histologic picture characterized by Reed-Sternberg cells.

A second experimental entity which bears some resemblance to Hodgkin's disease is the wasting condition observed in thymectomized animals (25, 49, 54, 72) which is characterized by lymphocytopenia, severe depletion of tissue lymphocytes (but not plasma cells), diarrhea, wasting and death. While the point has not been definitely proven, recent evidence, particularly the absence of wasting in thymectomized germ-free animals (45) points to an infectious etiology of this syndrome. Decreased resistance to infection is to be anticipated since in several species the neonatally thymectomized animal or the irradiated-thymectomized adult (7, 50) is immunologically impaired. In the best-studied animal, the mouse (25, 49), neonatal thymectomy leads to a depression of antibody formation and homograft rejection, and similar findings are observed in the rat (72), where delayed hypersensitivity is depressed also.

The specific question with regard to Hodgkin's disease is what relationship, if any, there is between the thymectomy-wasting syndrome and the humman condition. The similarity of two wasting diseases of lymphoid origin with associated immunological impairment is obvious. Lymphoid depletion and the susceptibility to secondary infection offer further analogies. However, the thymectomy-wasting syndrome again would not seem to account for the form of presentation of localized Hodgkin's disease, the histologic picture (Reed-Sternberg cells) or the chills, fever, and leukocytosis of disseminated disease. Furthermore, in the neonatally thymectomized animal, in contrast to the Hodgkin's patient, lymphocyte depletion frequently occurs early and depression of antibody formation may parallel the depression of delayed hipersensitivity.

Despite these several objections, the recent elucidation of thymus function does seem to bring nearer comprehension of the immunological defect of the Hodgkin's patient. Perhaps neonatal thymectomy and

Hodgkin's disease lead to a similar end stage of lymphoid and immunological exhaustion, but of different causation. (In this connection the parallel between the Swiss form of agammaglobulinemia (23, 27), a condition characterized by lymphocytopenia, thymic hypoplasia, frequent bacterial and **fungal** infections and early death, and the immunological state of the patient with advanced Hodgkin's disease should be recalled). Certainly it is unlikely, at least in the majority of Hodgkin's patients, that the thymus is the primary seat of the disease process (55) as Thomson has suggested (69), nor would this explain the defect. The little available direct evidence has failed to substantiate frequent thymus involvement early in Hodgkin's disease (43), and thymectomy beyond the neonatal period does not lead to early or severe immunologic impairment without an additional manipulation to deplete lymphoid tissue drastically (7, 50, 76). However, it is perhaps that immunological function which the thymus subserves which is impaired in Hodgkin's disease. As more is learned of the mechanism of thymic function (17) and delayed hypersensitivity, this idea may be formulated with more precision.

TABLE I
CUTANEOUS RESPONSE TO DELAYED ALLERGENS
(Modified from Schier *et al., Am. J. Med. 20*: 94, 1956)

Group	No.	Mumps	Candida albicans	Trichophyton gypseum	P.P.D.
Controls	79	90%	92%	68%	71%
Hodgkin's disease	43	14%	19%	16%	23%

TABLE II
COMPARISON OF THE INCIDENCE OF ANERGY AMONG PATIENTS IN GOOD OR POOR CONDITION
(Modified from Lamb *et al., J. Immunol. 89*: 555, 1962)

Group	Good Condition			Poor condition		
	No. Tested	No. Anergic	Per cent Anergic	No. Tested	No. Anergic	Per cent Anergic
Control	208	3	1.4			
Hodgkin's	49	26	53	8	7	88
Carcinoma	27	0	0	32	12	38
Leukemia	25	3	12	10	5	50
Non-Hodgkin's Lymphoma	20	1	5	21	13	62

TABLE III
SUMMARY OF DINITROCHLOROBENZENE TESTING IN HODGKIN'S DISEASE (1)

	Inactive disease	Active disease
No. of patients	15	25
No. of tests	20	40
Positive	14	0
Equivocal	1	0
Negative (Anergic)	5	40

TABLE IV

LYMPHOCYTE TRANSFER REACTION IN HODGKIN'S RECIPIENTS (3)

Recipient (Condition)	Donor	Millimeters of induration		
		48 hours	7 days	11-14 days
HD-1 (Good)	N-1	7	14	
	N-2	5	10	
	HD-2	7	0	
HD-2 (Good)	N-1	6	8	6
	N-3	5	5	?4
	HD-3	8	0	0
	HD-4	4	0	0
HD-4 (Good)	N-1	8	9	9
	N-2	5	8	6
	HD-3	3	0	0
	HD-5	3	0	0
HD-6 (Poor)	N-1	0	4	
	N-2	2	8	
	HD-1	2	0	
	HD-3	0	0	
HD-7 (Poor)	N-1	2	0	8*
	HD-8	4	2	0

Abbreviations: N = normal, HD = Hodgkin's disease

* Induration undiminished at 21 days

TABLE V

INFECTIOUS COMPLICATIONS IN HODGKIN'S DISEASE

(Modified from Casazza, Duvall, and Carbone,

Cancer Research 26: 1290, 1966)

Type of infection		No. of episodes in 51 patients
I	Bacterial	56
	A. Septicemia (from lung, skin and G.I. tract)	10
	1. *H. Staphylococcus aureus*	
	2. *Pseudomonas sp.*	5
	3. *E. coli sp.*	5
	4. *Streptococcus sp.*	2
	5. *Klebsiella sp.*	1
	6. *Proteus sp.*	1
	7. Paracolon bacillus	1
	8. Mixed gram-negative	3
	9. *H. Staph.* and gram-negative	1
	B. Pneumonia (*H. Staph.*, gram-negative and one pneumococcus)	14
	C. Enteritis (*Salmonella*)	4
	D. Urinary tract	4
	E. Skin abcesses	4
	F. Miscellaneous	1
II.	Viral infection	17
	A. Herpes zoster	8
	B. Varicella	1
	C. Cytomegalovirus	5
	D. Herpes simplex	3
III.	Fungal infections	10
	A. Disseminated	4
	1. *Cryptococcus*	
	2. *Histoplasma*	1
	3. Nocardia	1
	B. Localized	
	1. Pulmonary (*Nocardia* and *Candida*)	2
	2. Gastrointestinal (*Candida*)	2
IV.	Miscellaneous infections	3
	A. *Mycobacterium*	1
	B. *Toxoplasma*	1
	C. *Pneumocystis c.*	1
	TOTAL	86

TABLE VI

IMMUNOLOGICAL UNRESPONSIVENESS AND DISEASE STATUS

IN HODGKIN'S DISEASE

Disease status	Delayed hypersensitivity							
	Delayed allergens	Active sensitization (DNCB)	Antibody	Gamma globulin	Lymphocyte count	Lymphocyte transfer reaction	Lymphocyte function *in vitro*	Resistance to fungal, viral and bacterial agents
Localized (Inactive or healed)	N	N	N	N	N	N	N	N
Localized (Active)	↓	↓	N?	N	N or ↓	↓	?	N?
Generalized	↓ or ↓↓	↓	N?	N	↓ or ↓↓	↓	↓	↓
Terminal	↓↓	↓	↓	↓	↓↓	↓↓	↓	↓↓

Abbreviations: DNCB = dinitrochlorobenzene, N = normal, ↓ = depressed, and ↓↓ = markedly depressed.

REFENRENCES

1 — AISENBERG, A. C. — Studies on delayed hypersensitivity in Hodgkin's disease. *J. Clin. Invest. 41*: 1964-1970, 1962.

2 — AISENBERG, A. C. — Hodgkin's disease — Prognosis, treatment and etiologic and immunologic considerations. *270*: 508-514, 565-570, 617-622, 1964.

3 — AISENBERG, A. C. — Studies of lymphocyte transfer reactions in Hodgkin's disease. *J. Clin. Invest. 44*: 555-564, 1965.

4 — AISENBERG, A. C. — Manifestations of immunologic unresponsiveness in Hodgkin's disease. *Blood 25*: 1037-1042, 1965.

5 — AISENBERG, A. C. — Manifestations of immunologic unresponsiveness in Hodgkin's disease. *Cancer Research 26*: 1152-1160, 1966.

6 — AISENBERG, A. C. and LESKOWITZ, S. — Antibody formation in Hodgkin's disease. *New Eng. J. Med. 268*: 1269-1292, 1963.

7 — AISENBERG, A. C. and WILKES, B. — Immunologic status of thymectomized adult rats. *J. Immunol. 93*: 75-80, 1964.

8 — ARENDS, T., COONRAD, C. V., and RUNDLES, R. W. — Serum proteins in Hodgkin's disease and malignant lymphoma. *Am. J. Med. 16*: 833-841, 1954.

9 — BARR, M. and FAIRLEY, G. H. — Circulating antibodies in reticuloses. *Lancet 1*: 1305-1310, 1961.

10 — BEILBY, J. O. W., CADE, I. S., JELLIFFE, A. M., PARKIN, D. M., and STEWART, J. W. — Prolonged survival of a bone marrow graft resulting in blood-group chimera. *Brit. Med. J. 1*: 96-99, 1960.

11 — BILLINGHAM, R. E., DEFENDI, V., SILVERS, W. K., and STEINMULLER, D. — Quantitative studies on the induction of tolerance of skin hemografts and on runt disease in neonatal rats. *J. Nat. Cancer Inst. 28*: 365-435, 1962.

12 — BILLINGHAM, R. E., and SILVERS, W. K. — Sensitivity to hemografts of normal tissues and cells. *Am. Rev. Microbiol. 17*: 531-564, 1963.

13 — CASAZZA, A. R., DUVALL, C. P., and CARBONE, P. P. — Summary of infectious complications occurring in patients with Hodgkin's disease. *Cancer Research 26*: 1290-1296, 1966.

14 — CHASE, M. W. — Delayed-type hypersensitivity and the immunology of Hodgkin's disease, with a parallel examination of sarcoidosis. *Cancer Research 26*: 1907-1120, 1966.

15 — COLLINS, V. P., GELLHORN, A., and TRIMBLE, J. R. — The coincidence of cryptococcosis and disease of the reticulo-endothelial systems. *Cancer 4*: 883-885, 1951.

16 — CONE, L., and UHR, J. W. — Immunological deficiency disorders associated with chronic lymphatic leukemia and multiple myeloma. *J. Clin. Invest. 43*: 3341-2248, 1964.

17 — COOPER, M. D., PETERSON, R. D. A., GABRIELSEN, A. E., and GOOD, R. A. — Lymphoid malignancy and development, differentiation and function of the lymphoreticular system. *Cancer Research 26*: 1165-1169, 1966.

18 — DUBIN, I. N. — Poverty of immunological mechanism in patients with Hodgkin's disease. *Ann. Int. Med. 27*: 898-913, 1947.

19 — EWING, J. — *Neoplastic Disease*: A treatise on tumors. Fourth edition. 1160 pp. Philadelphia: Saunders, 1940.

20 — FAIRLEY, G. H., and AKERS, R. J. — Antibodies to blood group A and B substances in reticuloses. *Brit. J. Hem. 8*: 375, 1962.

21 — GELLER, W. — Study of antibody formation in patients with malignant lymphomas. *J. Lab. and Clin. Med. 42*: 232-237, 1953.

22 — GENDEL, B. R., ENDE, M., and NORMAN, S. L. — Cryptococcosis — A review with special refecence to apparent association with Hodgkin's disease. *Am. J. Med.* 9: 343-355, 1950.

23 — GITLIN, D., and CRAIG, J. M. — Thymus in agammaglobulinemia. *Pediatrics 32*: 517-530, 1963.

24 — GITLIN, D., JANEWAY, C. A., ASP, L., and CRAIG, J. M. — Agammaglobulinemia. *In* Cellular and Humoral Aspects of the Hypersensitive State, H. S. LAWRENCE, ed. NEw York, Hoeber-Harper, 1959; pp. 375-441.

25 — GOOD, R. A., DALMASSO, A. P., MARTINEZ, C., ARCHER, O. K., PIERCE, J. C., and PAPERMASTER, B. E. — The role of the thymus in development of immunologic capacity in rabbits and mice. *J. Exp. Med. 116*: 773-796, 1962.

26 — GOOD, R. A., KELLEY, W. D., ROTSTEIN, J., and VARCO, R. I. — Immunological deficiency diseases. *Prog. Allergy 6*: 187-319, 1962.

27 — GOOD, R. A., MARTINEZ, C., and GABRIELSON, A. E. — Clinical considerations of the thymus in immunology. *In* The Thymus in Immunology, R. A. Good and A. E. Gabrielson, eds. New York: Hoeber-Harper, 1964, pp. 3-47.

28 — GOWANS, J. I., and McGREGOR, D. D. — The immunological activity of lymphocytes. *Prog. Allergy 9*: 1-78, 1965.

29 — GRAY, J. G., and RUSSEL, P. S. — Donor selection in human organ transplantation. *Lancet 2*: 863-865, 1963.

30 — GREEN, I., INKELAS, M., and ALLEN, L. B. — Hodgkin's disease — a maternal-to-foetal lymphocyte chimaera? *Lancet 1*: 30-32, 1960.

31 — GROSS, L. — Immunological defect in aged populations and its relation to cancer. *Cancer 18*: 201-204, 1965.

32 — HERSH, E. M., and OPPENHEIM, J. J. — Impaired *in vitro* lymphocyte transformation in Hodgkin's disease. *New Eng. J. Med. 273*: 1006-1012, 1965.

33 — HOFFMAN, G. T., and ROTTINO, A. — Studies of immunological reactions of patients with Hodgkin's disease: antibody reaction to typhoid immunization. *Arch. Int. Med. 86*: 872-876, 1950.

33[a] — HOLM, G., PERLMANN, P., and JOHANSSON, B. — Impaired phytohemagglutinin-induced cytotoxicity *in vitro* of lymphocytes from patients with Hodgkin's disease or chronic lymphocytic leukemia. *Information Exchange Group* No. 5, No. *273*: 1966.

34 — JACKSON, H., Jr., and PARKER, F., Jr. — Hodgkin's Disease and Allied Disorders. New York, Oxford Press, 1947.

35 — KAPLAN, H. S., and SMITHERS, D. W. — Autoimmunity in man and homologous disease in mice in relation to the malignant lymphomas. *Lancet 2*: 1-4, 1959.

36 — KELLY, W. D., LAMB, D. L., VARCO, R. L., and GOOD, R. A. — An investigation of Hodgkin's disease with respect to the problem of homotransplantation. *Ann. N.Y. Acad. Sci. 87*: 187-202, 1960.

37 — KLIGMAN, A. M., EPSTEIN, W. L. — Some factors affecting contact sensitization in man. *In* Mechanisms of Hypersensitivity, J. H. Shaffer, G. A. LoGrippo, and M. W. Chase, eds. Boston: Little, Brown, 1959, pp. 713-722.

38 — LAMB, D., PILNEY, R., KELLY, W. D., and GOOD, R. A. — A comparative study of the incidence of anergy in patients with carcinoma, Hodgkin's disease and other lymphomas. *J. Immunol. 89*: 555-558, 1962.

39 — LARSON, D. L., and TOMLINSON, L. J. — Quantitative antibody studies in man. III. Antibody response in leukemia and other malignant lymphomata. *J. Clin. Investigation 32*: 317-321, 1953.

40 — LEVIN, A. G., CUSTODIO, D. B., MANDEL, E. E., and SOUTHAM, C. M. — Rejection of cancer homotransplants by patients with debilitating non-neoplastic disease. *Ann. N.Y. Acad. Sci. 120*: 410-423, 1964.

41 — LEVIN, A. G., McDONOUGH, E. F., Jr., MILLER, D. G., and SOUTHAM, C. M. — Delayed hypersensitivity to DNFB in sick and healthy persons. *Ann. N.Y. Acad. Sci. 120*: 400-409, 1964.

42 — LOUTIT, J. F. — Immunological and trophic functions of lymphocytes. *Lancet 2*: 1106-1108, 1962.

43 — MARSHALL, A. H. E., and WOOD, C. — The involvement of the thymus in

Hodgkin's disease. *J. Path. Bact. 73*: 163-166, 1957.

44 — McBRIDE, R. A. — Graft-versus-host reaction in lymphoid proliferation. *Cancer Research 26*: 1135-1151, 1966.

45 — McINTIRE, K. R., -SELL, S., and MILLER, J. F. A. P. — Pathogenesis of post-thymectomy wasting syndrome. *Nature 704*: 151-155, 1964.

46 — McKELVEY, E. M., and FAHEY, J. L. — Immunoglabulin changes in disease: Quantitation on the basis of heavy polypeptide chains, IgG (yG), IgA (yA), and IgM (yM), and light polypeptide chains, type K (I) and type L (II). *J. Clin. Invest. 44*: 1778-1787, 1965.

47 — MILLER, D. G. — Patterns of immunological deficiency in lymphomas and leukemias. *Ann. Int. Med. 57*: 703-716, 1962.

48 — MILLER, D. G. LIZARDO, J. G., and SNYDERMAN, R. — Homologous and heterologous skin transplantation in lymphomatous disease. *J. Nat. Cancer Inst. 26*: 569-579, 1961.

49 — MILLER, J. F. A. P. — Effect of neonatal thymectomy on the immunological responsiveness of the mouse. *Proc. Roy. Soc. (Biol.) 156*: 415-428, 1962.

50 — MILLER, J. F. A. P., DOAK, S. M. A., and CROSS, A. M. — Role of the thymus in recovery of the immune mechanisms in the irradiated adult mouse. *Proc. Soc. Exp. Biol. Med. 112*: 785-792, 1963.

51 — MILLIAN, S. J., MILLER, D. G., and SCHAEFFER, M. — Viral complement-fixing antibody in patients with Hodgkin's disease, lymphosarcoma, reticulum cell sarcoma and chronic lymphatic leukemia. *Cancer 18*: 674-678, 1965.

52 — MITCHELL, A. G., WHERRY, W. B., EDDY, B., and STEVENSON, F. E. — Studies in immunity — I. Nonspecific factors influencing the reaction of the skin to tuberculin. *Am. J. Dis. Child. 36*: 720-724, 1928.

53 — PARKER, F., Jr., JACKSON, H., Jr., FITZHUGH, G., and SPIES, T. D. — Studies of diseases of lymphoid and myeloid tissues — IV. Skin reactions to human and avian tuberculin. *J. Immunol. 22*: 277-282, 1932.

54 — PARROTT, D. M. V., and EAST, J. — Role of the thymus in neonatal life. *Nature 195*: 347, 1962.

55 — PATEY, D. H. — A contribution on the study of Hodgkin's disease. *Brit. J. Surg. 50*: 389-393, 1953.

56 — PETERS, M. V., and MIDDLEMISS, K. C. H. — Study of Hodgkin's disease treated by irradiation. *Am. J. Roentgenol. 79*: 114-121, 1958.

57 — RAZIS, P. V., DIAMOND, H. D., and CRAVER, L. F. — Hodgkin's disease associated with other malignant humors and certain nonmalignant diseases. *Am. J. Med. Sci. 238*: 327-335, 1959.

58 — ROSENTHAL, S. R. — Significance of tissue lymphocytes in the prognosis of lymphogranulomatosis. *Arch. Path. 21*: 628-646, 1936.

59 — SAMTER, M. — Eosinophils. *In* Immunological Diseases, M. Samter, H. L. Alexander, D. W. Talmage, B. Rose, W. B. Sherman, and J. H. Vaughan, eds. Boston, Little, Brown, 1965, pp. 242-245.

60 — SASLAW, S., CARLISLE, H. D., and BOURONCLE, B. — Antibody response in hematologic patients. *Proc. Soc. Exp. Biol. Med. 106*: 654, 1961.

61 — SCHIER, W. W. — Cutaneous anergy and Hodgkin's disease. *New Eng. J. Med. 250*: 353-361, 1954.

62 — SCHIER, W. W., ROTH, A., OSTROFF, G., and SCHRIFT, M. H. — Hodgkin's disease and immunity. *Am. J. Med. 20*: 94-99, 1956.

63 — SCHWARTZ, R. S., and BELDOTTI, L. — Malignant lymphomas following allogenic disease — transition from an immunological to a neoplastic disorder. *Science 149*: 1511-1514, 1965.

64 — SIMONSEN, M. — Graft versus host reaction — Their natural history, and applicbility as tools of research. *Prog. Allergy 6*: 349-467, 1962.

65 — SOKAL, J. E. — Immunologic defects in Hodgkin's disease. *Cancer Research 26*: 1161-1164, 1966.

66 — SOKAL, J. E., and PRIMIKIRIOS, N. — The delayed skin test response in Hodgkin's disease and lymphosarcoma

— Effect of disease activity. *Cancer 14*: 597-607, 1961.

67 — STARR, S., and BERKOVICH, S. — Effect of measles, gamma-globulin-modified measles and vaccine measles on the tuberculin test. *New Eng. J. Med. 27*: 394-397, 1964.

68 — STEINER, P. E. — Etiology of Hodgkin's disease. II. Skin reaction to avian and human tuberculin proteins in Hodgkin's disease. *Arch. Intern. Med. 54*: 11-17, 1934.

69 — THOMSON, A. D. — The thymic origin of Hodgkin's disease. *Brit. J. Cancer 9*: 37-50, 1955.

70 — ULTMANN, J. E., CUNNINGHAM, J. K., and GELLHORN, A. A. — Hodgkin's disease — The clinical picture. *Cancer Research 26*: 1047-1060, 1966.

71 — ULTMANN, J. E., FISH, W., OSSERMAN, E., and GELLHORN, A. — The clinical implications of hypogammaglobulinemia in patients with chronic lymphocyte leukemia and lymphocytic lymphosarcoma. *Inn. Intern. Med. 51*: 501-516, 1959.

72 — WAKSMAN, B. H., ARNASON, B. G., and JANKOVIC, B. D. — Role of the thymus in immune reactions in rats. *J. Exp. Med. 116*: 159-206, 1962.

73 — WILLIAMS, H. W., DIAMOND, H. D., CRAVER, L. F., and PARSONS, H. — Neurological Complications of Lymphomas and Leukemias. Springfield, 111., Charles C. Thomas, 1959.

74 — WISEMAN, B. K. — The blood pictures in the primary diseases of the lymphatic system. *J.A.M.A.* 107: 2016-2022, 1936.

75 — ZIMMERMAN, L. E., and RAPPAPORT, H. — Occurrence of cryptococcosis in patients with malignant disease of the reticuloendothelial system. *J. Clin. Path. 24*: 1050-1072, 1954.

76 — ZOLLINGER, R. M., Jr., LINDEM, M. C., Jr., FILLER, R. M., CORSO, J. M., and WILSON, R. E. — Effect of thymectomy on skin-homograft survival in children. *New Eng. J. Med. 270*: 707-710, 1964.

PATHOLOGICAL ASPECTS OF HODGKIN'S

DR. ROBERT J. LUKES

INTRODUCTION

The unique diversity of the morphologic features in Hodgkin's disease and the variable rates of progression of the disease have evoked an almost unparalleled variety of terms in an attempt to relate the histologic features to survival and to depict the as yet unsettled nature of the basic process. Over 50 terms for the disease were collected from the literature by Wallhauser from the 1st century after Thomas Hodgkin's description. This profusion of names for the disease primarily reflects the different concepts of the disease particularly in relationship to etiology. The noncommittal eponymic designation has gained general acceptance in the United States at the present time, even though the process is generally regarded as a neoplasm and included with the malignant lymphomas. In the past 4 decades numerous terms have been proposed for the histologic types of Hodgkin's disease as a result of the attempts to relate the histologic changes to the extremely variable rates of progression of the disease and to provide a prognostic basis for the recognition of potential prolonged survivors.

Interest in the importance of the histologic findings in prognosis was initiated by Rosenthal when he demonstrated the relationship between lymphocytic proliferation and slowly progressive disease and stressed the importance of the frequency of lymphocytes in prognosis. Earlier Ewing proposed the term "sarcoma" for a pleomorphic neoplastic proliferation of Reed-Sternberg cells. The classical histologic types of Jackson and Parker, namely paragranuloma, granuloma, and sarcoma, are related to many of the findings of Ewing and Rosenthal. Subsequently the prognostic importance of the predominant lymphocytic lesions has been supported by a number of observers, although a variety of terms have been suggested for the association of lymphocytic proliferation with prolonged survival. Neither Croizat et al. nor Winterhalter, however, found definite evidence of a relationship between the course of the disease and the histologic features.

The importance of clinical staging in Hodgkin's disease as iniitally defined by Peters and later refined by Peters and Middlemiss emphasized the prognostic importance of localized manifestation in

Hodgkin's disease and provided the basis for the recent proposal of the possibility of cure in Hodgkin's disease. The significance of the histologic features in untreated Hodgkin's disease in relationship to the clinical stages and survival was re-evaluated in our recent study of the World War II cases of Hodgkin's disease in a 15 to 18 year follow-up study. The results of this study re-emphasized the importance of the lymphocyte in Hodgkin's disease and its inverse relationship to Reed-Sternberg cells, and demonstrated a definite relaitonship between the histologic features and the clinical stages existing at the time of biopsy. A new histologic type, nodular sclerosis, emerged as an important prognostic group and the regional expression of Hodgkin's disease in the anterior superior mediastinum.

In this presentation I will attempt to define and demonstrate the histologic variations in Hodgkin's disease and relate our terminology for these variations to the wide variety of terms that have been employed in the past. An attempt also will be made to relate the histologic findings to the gross pathologic changes and the evolution of the disease process. In the next presentation the apparent relationship between the histologic findings and clinical stages and the significance in prognosis will be presented.

MORPHOLOGY

The diversity of the morphologic findings in Hodgkin's disease is well known and the association of abnormal reticulum cell proliferation of the Reed-Sternberg cell type with a variable inflammatory type cellular proliferation represents a unique histologic process. The nature of this process has puzzled pathologists since the initial histologic description of Greenfield. Investigators in the past few decades have been primarily concerned with the evaluation of the histologic findings in prolonged survival cases for prognostic purposes, and little attention has been given to the study of the significance of the numerous variations in the histologic findings, although the process is generally regarded as neoplastic in the United States.

Classification of Hodgkin's disease as a neoplasm is based on the generally progressive character of the process, the occasional pleomorphic appearance of the Reed-Sternberg cell, and the tumor-like disseminated masses observed at autopsy that may exhibit infiltrative features. The indistinguishable appearance at times of the histologic findings of the fulminating terminal phase of Hodgkin's disease with those of histiocytic lymphoma (reticulum cell sarcoma) has been used as further support for the neoplastic nature of the process. The critical point appears to revolve about the debatable issue whether the Reed-Sternberg cell is a neoplastic cell or simply a modified reticulum cell that at times may become pleomorphic—at which time it is definitely neoplastic. The common occurrence of numerous abnormal reticulum cells, without the distinctive features of classical Reed-Sternberg cells, that appear to represent intermediate or partially developed established whether the process, if neoplastic, involves all the cellular components and is a mixed lymphoma as proposed by Lumb, Berman and others, or (**slide**) the Reed-Sternberg cell is the only neoplastic component—if indeed it is a neoplastic cell—and the associated histologic components are inflammatory reactions.

Definite evidence of neoplasia is observed as a sarcomatous type in a small proportion of cases at biopsy with fulminating disease and a limited number of cases at autopsy where Reed-Sternberg cells predominate and are distinctly pleomorphic. Biopsy specimens in the majority of cases exhibit morphologic expressions of an inflammatory process associated with an increase in the frequency of the Reed-Sternberg cells and a decrease in lymphocytes and other cellular elements with progressive disease. The change in character of the Reed-Sternberg cells with the development of distinctive pleomorphic features provides a basis for suggesting that the evolution of the Hodgkin's disease process may represent the induction of malignant neoplasia. In this situation the cellular and connective tissue components associated with the Reed-Sternberg cells would represent expressions of the host's attempt to counteract the induction of neoplasia. This consideration fits

well with the associated variable cellular proliferation and the inverse relationship between lymphocytes and Reed-Sternberg cells. The possibility of neoplastic induction in Hodgkin's disease is unanswerable at the present time, but requires thorough consideration and investigation.

The reticulum cell proliferation in Hodgkin's disease involves not only the abnormal reticulum cell of the Reed-Sternberg cell type and its variants, but also a reactive histiocyte that is possibly related to the formation of fibrillar reticulum, the fibroblastic component and eventually fibrous connective tissue. A variety of Reed-Sternberg cells usually can be found in an individual biopsy or autopsy specimen. The frequency and character of Reed-Sternberg cells in our experience appears to be related in some degree to the type of associated cellular proliferation. Only a few variations of Reed-Sternberg cells, however, can be regarded as diagnostically reliable, since benign proliferation of reticulum cells in reactive processes, especially in viral infections, may exhibit large nucleoli and vesicular nuclei, 2 features often associated with Reed-Sternberg cells. Fortunately multinucleation does not appear to be a feature of the reticulum cell reaction in viral infections, and provides a basis for their differentiation. The 2 most distinctive and reliable features in the identification of Reed-Sternberg cells are the huge inclusion-like nucleolus and polyploidism, the occurrence of multiple divisions of the nuclei without cytoplasmic division. A few of the more common variations in Reed-Sternberg cells are presented in the **next slide.** Mononuclear forms are usually found in typical lesions of Hodgkin's disease and also may exhibit the huge inclusion-like nucleolus and a vesicular nucleus. Although the mononuclear type appears to represent a form of the Reed-Sternberg cell, it is not considered to be reliable diagnostically in our experience since it may be confused with the reticulum cells of viral reactions.

Lobated and binucleated forms represent manifestations of polyploidism, one of the important distinctive features of Reed-Sternberg cells. A peculiar clear zone about the huge nucleolus is another unusual feature of these cells and presents the nucleus with a vesicular appearance, but it is uncertain whether or not this feature is artifactual. The nuclear chromatin may be delicate and lacy, but it is usually observed to be compressed at the periphery, at times as a thickened nuclear membrane with a clear halo-like space about the nucleolus. The nucleolus typically is large, almost spherical in appearance, and resembles an inclusion body with a smooth margin. In staining character it varies from eosinophilic to amphophilic, but is of uniform intensity. The cytoplasm is rather inconsistent, both in quantity and staining, although it is most frequently observed to be abundant and lightly eosinophilic to amphophilic. The pleomorphic Reed-Sternberg cell that is regarded as sarcomatous is an unusually large cell with a tendency to extraordinary lobular nuclear variations and multinucleation that appear to represent an extreme degree or polyploidism.

HISTOLOGIC TYPES

Numerous histologic types have been described in the past 3 decades primarily in an attempt to account for the cases with slowly progressive disease or prolonged survival with asymptomatic disease. In our recent study in which the significance of the histologic features and clinical stages in Hodgkin's disease was evaluated, it was apparent that there were 6 predominant histologic expressions of untreated Hodgkin's disease for which we have proposed the following terms (**slide**):
(a) lymphocytic and/or histiocytic (L & H), diffuse; (b) (**slide**) lymphocytic and/or histiocytic (L & H), nodular; (c) mixed; (d) nodular sclerosis; (e) diffuse fibrosis; (f) reticular. In the following discussion the more commonly employed types described in the literature will be analyzed in comparison with the 6 predominant histologic expressions of Hodgkin's disease.

HISTOLOGIC FINDINGS

Variation in the major components within each histologic type is demonstrated schematically in Table 4 on the basis of 1 to 10 + with each plus representing approximately 10%. It should be emphasized that

the quantitation of Reed-Sternberg cells although only a small proportion of those included may exhibit classical diagnostic features. In addition, the components unquestionable at times may exhibit more variation than the degree indicated, particularly in the nodular sclerosis and mixed types. These general estimations of the histologic components in the various types illustrate several important basic features of the histologic process in Hodgkin's disease.

In general there is an inverse relationship between the frequency of lymphocytes and Reed-Sternberg cells, particularly the diagnostic cells. The lymphocytic proliferation of the L & H types is associated with a small proportion of Reed-Sternberg cells while in the diffuse fibrosis and reticular types, the depletion of lymphocytes is associated with numerous Reed-Sternberg cells. Connective tissue is observed in 2 distinctive forms: (a) orderly distributed interconnecting collagen bands in nodular sclerosis and (b) irregularly distributed finely fibrillar connective tissue or compact proteinaeous material that resembles pre-collagen in diffuse fibrosis. Diffuse fibrosis is associated with lymphocytic depletion.

LYMPHOCYTIC AND/OR HISTIOCYTIC PROLIFERATION

There is general agreement on the existence of a histologic lesion composed predominantly of mature lymphocytes. Although the term "paragranuloma" is commonly used in the United States, numerous terms have been proposed. In addition, lymphocytic proliferation in Hodgkin's disease occurs usually in association with varying numbers of reactive histiocytes that are readily differentiated from the variants of the Reed-Sternberg cell. The histiocytic component varies widely from scattered individual histiocytes to a predominance of histiocytes with only a small component of residual lymphocytes. The lesion composed predominantly of lymphocytes has been the subject of numerous reports, while the lesion where the histiocytic component is dominant has been overlooked and apparently included within the granuloma group. The term lymphocytic and/or histiocytic (L & H) was considered most appropriate because of the almost constant occurrence of histiocytes in lymphocytic proliferations, the frequency of lesions with a predominance of histiocytes, and the wide spectrum of lymphocytic or histiocytic proliferation observed in this group.

With this spectrum of lymphocytic and histiocytic proliferation, characteristic Reed-Sternberg cells are rare, although the peculiar abnormal polyploid reticulum cells previously discussed with Reed-Sternberg cells may be relatively numerous. Eosinophils, plasma cells, and nature neutrophils are uncommon or absent. There is essentially no fibrosis.

LYMPHOCYTIC AND/OR HISTIOCYTIC (L & H) TYPE, DIFFUSE

(**Slide**) In the diffuse L & H type the cellular proliferation extends uniformly throughout the lymph node with compression of sinusoids and absence of lymphatic follicles. In this example lymphocytes predominate and small clusters of pale histiocytes are seen irregularly distributed throughout the lymph node as a minor component. The capsule is uninvolved.

(**Slide**) In this higher magnification it is apparent that the lymphocytic proliferation is well differentiated, and the occasional histiocytes appear as large cells with abundant pale, lightly eosinophilic cytoplasm and small nuclei. Cells resembling Reed-Sternberg cells are not apparent in this area. When the lymphocytic component predominates in the diffuse type and histiocytes are infrequent or rare, the lesion may closely resemble a well differentiated lymphocytic lymphoma, the tissue counterpart of chronic lymphocytic leukemia. The two processes are differentiated histologically on the basis of an essentially single cell type of proliferation, the small lymphocyte, in lymphocytic lymphoma, with only a rare reticulum cell or other cellular elements. In addition, this lymphoma occurs predominantly in patients over 55 years of age, and rarely under 45 years. The diffuse L & H type, by contrast, usually has a histiocytic component to some degree and numerous abnormal reticulum cells related to Reed-Sternberg cells and occurs predo-

minantly in younger patients. The abnormal reticulum cell component that appears to be related to the Reed-Sternberg cells is often relatively prominent, as in this high magnification field, and may represent as much as 10% of the cell population. These peculiar large cells have folded, twisted, lobated pale nuclei, fine, lacy, delicate chromatin and small nucleoli. Characteristic Reed-Sternberg cells with large nucleoli are extremely infrequent in this lesion. It may be necessary to search a number of sections to find typical Reed-Sternberg cells on which to establish reliable diagnosis. In this field the distinctive reactive character of the large pale cytoplasmic reactive histiocytes can be readily differentiated from the partially modified polyploid reticulum cells that appear to be related to Reed-Sternberg cells.

(**Slide**) In this table, the numerous terms that have been proposed in literature for the predominantly lymphocytic proliferation observed in Hodgkin's disease, are listed in association with the author and year of publication.

It is readily apparent that this group has aroused most of the attention of pathologists as a result of its distinctive histologic character and the association of lymphocytic proliferation with prolonged survival. It should be emphasized that the terms listed refer to a predominant lymphocytic proliferation with a small component of histiocytes where eosinophils and plasma cells were infrequent or absent, and there was little or no fibrosis and necrosis was absent. Almost thirty years ago Rosenfeld recognized the prognostic significance of the predominant lymphocytic proliferation and the associated relative infrequency of Reed-Sternberg cells for which the term "L & R" (lymphocytic and reticulum cell) was proposed. Subsequently, Jackson suggested that this lesion might represent early Hodgkin's disease. Later Jackson and Parker indicated that this was an unfortunate choice of terms and recommended paragranuloma as a more appropriate definition to indicate a close relationship to Hodgkin's granuloma. The term "lymphoreticular medullary reticulosis" was proposed several years later by Robb-Smith apparently for the same lesion. The high incidence of survivors at 5 and 10 years and good prognosis of this lesion prompted the proposal of the term "benign Hodgkin's" by Harrison in 1951 in preference to the term "paragranuloma." It evolved from a retrospective study of cases with prolonged survival in this group.

Histologically, the lesion was composed predominantly of small lymphocytes with a prominent component of abnormal reticulum cells. Subdivision of the cellular proliferation by either collagen bands or reticulum fibers into cellular nodules was a common feature. It appears from their photomicrographs and description that the majority of their cases may represent the cellular phase of the nodular sclerosing type with limited collagen formation. This lesion will be considered in a subsequent section. The study was subsequently enlarged, again, under the term "benign Hodgkin's disease" by Dawson and Harrison. A similar cellular proliferation was observed in nodular distribution in this series in approximately 2/3 of their cases in association with compression of reticulum fibers about the periphery of the nodules. The resemblance of the nodular proliferation to the type of follicular lymphoma described by Rappaport, et al was noted. The term "reticular lymphoma" was urged by Lumb to emphasize its distinctive character and definite relation to Hodgkin's disease. Symmers prefers the term **"indolent"** to emphasize the need for caution in prognosis. Although he acknowledges its identity with paragranuloma.

LYMPHOCYTIC AND HISTIOCYTIC (L & H), NODULAR

(**Slide**) In this process the cellular proliferation is aggregated in a vaguely nodular fashion. The proliferation is usually overwhelmingly lymphocytic, involving both nodules and internodular tissue as in this lesion.

Histiocytes have predominated in the nodular type on only a few occasions in our experience.

The nodules are generally large, closely situated, and often involve only a portion of the lymph node. The individual nodules are vaguely outlined, but clearly demonstrated in a reticulum stain with compres-

sion of the reticulum fibers about the periphery of the nodules. Typical Reed-Sternberg cells are rare, although abnormal polyploid reticulum cells with small nucleoli may be numerous and tend to be concentrated in the central portion of the nodules.

(Slide) The nodular character of this type of Hodgkin's disease was initially demonstrated quite recently by Rappaport, et al under the term "follicular lymphoma, type V" Hodgkin's type in their classical study on the re-evaluation of follicular lymphoma. These authors indicated the lesion would be regarded as a paragranuloma if it had lacked nodularity. They also suggested that paragranuloma might be a more ideal designation rather than to include the lesion within the general group of lymphomas. Subsequently Dawson and Harrison and also Wright have emphasized the resemblance of many of their cases under the term "benign Hodgkin's" to the group described by Rappaport, et al.

LYMPHOCYTIC AND HISTIOCYTIC (L & H), DIFFUSE, HISTIOCYTES PREDOMINATING

(Slide) In this magnification of photomicrograph the diffuse L & H type of Hodgkin's disease where histiocytes predominate is demonstrated.

There is little or no fibrosis, essentially no admixture of eosinophils, plasma cells and no necrosis.

(Slide) The lesion is composed predominantly of histiocytes with a number of residual lymphocytes. Diagnostic Reed-Sternberg cells are usually infrequent and difficult to find as in the predominantly lymphocytic lesions.

(Slide) In the past this predominantly histiocytic lesion appears to have been included within the granuloma group of Jackson and Parker. Its importance appears to be dependent upon its relationship to the predominantly lymphocytic type and both in type of clinical disease and slow progression.

MIXED TYPE

(Next Slide) This histologic type is of heterogeneous composition and occupies a somewhat intermediate position between the predominantly lymphocytic proliferation at one extreme and lymphocytic depletion with diffuse fibrosis and reticular types at the other. As the name implies it is composed of a variety of histologic components, including histiocytes, mature neutrophils, eosinophils, plasma cells, histiocytes and lymphocytes in varying proportions, usually with a slight to moderate degree of disorderly fibrosis, but without collagen formation. The Reed-Sternberg cells and related abnormal reticulum cells are often rather numerous and prominent. Focal necrosis may be seen, but is usually not marked. The process generally extends throughout the entire lymph node and is associated with obliteration of lymphatic sinusoids and follicles. Focal involvement by a similar process, however, may extend throughout portions of a lymph node or be limited to small interfollicular areas, apparently as evidence of early involvement of the node. Delineation of this type from the L & H types at one extreme and the lymphocytic depletion types at the other at times may be difficult. It appears to depend primarily on the frequency and character of the Reed-Sternberg cells and the degree and character of fibrosis.

(Next Slide) The mixed type most closely approximates the classical concept of granuloma as presented by Jackson and Parker.

(Next Slide) Granuloma, unfortunately incorporates a variety of histologic expressions, including the prominent histiocytic proliferation and the advanced fibrosis types, and those where Reed-Sternberg cells predominate but are not sarcomatous. Thus, the granuloma group includes almost the whole spectrum of cellular proliferation. Fibromedullary reticulosis, the term of Robb-Smith, apparently represents a group comparable to the granuloma.

ADVANCED FIBROSIS

(Next Slide) The advanced degree of fibrosis in Hodgkin's disease through the years have been generally considered together although they appear from our study to represent two distinct types.

The first, nodular sclerosis, exhibits orderly bands of dense collageneous connec-

tive tissue that has a definite tendency to subdivide lymphoid tissue into isolated cellular nodules. The second, diffuse fibrosis, is characterized by disorganized type of fibrosis of variable character which may be composed of cellular fibroblastic connective tissue or hypocellular fibrillar connective tissue associated with cellular depletion, particularly of lymphocytes. Both types are generally included together in the granuloma group.

NODULAR SCLEROSIS

(Next Slide) This histologic type is characterized by orderly bands of interconnecting collagenous connective tissue that subdivides distinctly abnormal lymphoid tissue partially or entirely into isolated cellular nodules, as in this section of a mediastinal mass. The degree of collagen formation and the character of cellular proliferation vary widely at times, even within the same specimen.

(Next Slide) In this photomicrograph the typical nodule of nodular sclerosis is demonstrated. The celluar nodule is circumscribed by wide bands of dense collagen in the H & E section. While the trichrome stain on the right half demonstrates the collagenous nature of the connective tissue.

(Next Slide) The collagenous character of the circumscribing bands can readily be demonstrated on polarized light with ordinary H & E sections, as demonstrated in this photomicrograph.

(Next Slide) The cellular proliferation in nodular sclerosis, although varying widely is distinctive and exhibits similar variations both in the nodules and in the abnormal lymphoid tissue not subdivided by collagen. The distinctive feature of the cellular proliferation in nodular sclerosis is the unusually large variant of the Reed-Sternberg cell which has abudant, pale to water-clear slightly eosinophilic cytoplasm with well defined cellular borders that present the appearance of the Reed-Sternberg cells situated in a lacuna-like space. These cells have prominent, lobated nucleous often with numerous lobes, delicate, lacy nuclear chromatin and small to medium size nucleoli. Typical huge nucleoli are infrequent and often difficult to find. The numerous variations of the nodular sclerosing lesion will be discussed in detail later.

DIFFUSE FIBROSIS

(Next Slide) This type appears to represent primarily a histologic manifestation of cellular depletion in Hodgkin's disease involving all cell types with the exception of the Reed-Sternberg cell, and specifically involves the lymphocytes. Diffuse fibrosis is the common terminal histologic expression of untreated Hodgkin's disease and is associated usually with numerous Reed-Sternberg cells and focal necrosis. Is constitutes the typical findings noted at autopsy. Although therapy undoubtedly contributes to the cellular depletion and the fibrosis observed at autopsy, a similar lesion frequently is observed in biopsies, particularly from patients in untreated febrile stage III or IV disease. The fibrosis is somewhat variable in appearance, disorderly in reticulum fiber distribution and nonbirefringent in character. It is generally composed of compact, amorphous, proteinaceous appearing hypocellular material with a fibrillar character at times, and in general bears a resemblance to pre-collagen.

(Next Slide) On occasion the fibrosis may be partially or prominently fibroblastic. The process involves lymph nodes irregularly and small loosely cellular portions may remain that contain numerous Reed-Sternberg cells. Differentiation from nodular sclerosis is readily accomplished on the basis of the orderly collagen bands usually found surounding cellular nodules, and the distinctive large cytoplasmic Reed-Sternberg cells in the nodular sclerosing types. Diffuse fibrosis, by contrast, has disorderly, nonbinucleated connective tissue with cellular depletion.

(Next Slide) Advanced fibrosis in the past has always included both nodular sclerosis and diffuse fibrosis within a single group, most commonly under the term "granuloma." Many years ago Rosenthal separated a F and R type with prominent fibrosis and numerous reticulum cells, but it is difficult to determine whether he was referring to one or both lesions.

RETICULAR

(Next Slide) The term is employed to refer to the type of lesion in Hodgkin's disease that has a predominant component of Reed-Sternberg cells, although a mixture of cell types may remain. The lesion appears to be intimately related to diffuse fibrosis and also represent an expression of a lymphocytic depletion type. In includes lesions in which the Reed-Sternberg cells may either be pleomrphic and sarcomatous, according to the criteria of Jackson and Parker, or exhibit a simple numerical predominance of characteistic Reed-Sternberg cells. In the reticular type focal necrosis is common and at times a portion of the lymph node may exhibit features of diffuse fibrosis. The reticular type is most commonly observed in autopsy material of post therapy cases in which it represents almos the exclusive residual cell type, usually in association with some degree of diffuse fibrosis. It may be observed in lymph node biopsies from untreated cases in stage III or IV with systemic symptoms. The pleomorphic Reed-Sternberg cell proliferation that fulfills the definition of Hodgkin's sarcoma is very uncommon in our experience in untreated cases, and only 1% of the cases in our series exhibited this manifestation.

(Next Slide) The lesion where Reed-Sternberg cells numerically predominate have been included generally in the granuloma group, according to Jackson and Parker, although Lennert recently suggested the term "reticulo-Hodgkin's" and Rosenthal many years ago emphasized this lesion lymphocytes may be depleted.

THE RELATIONSHIP OF SURVIVAL TO HISTOLOGIC TYPES

(Next Slide) In this slide the frequency of the histologic types in our recent study of 377 U. S. Army cases which were followed for 15 years, is listed, along with the median survival and a number of survivals at 15 years. Nodular sclerosis with 149 cases or 40% is the most common histologic type. The remaining cases are distributed in a somewhat balanced fashion. The histologic types associaetd with lymphocytic proliferation, the nodular and diffuse L & H types contain 63 or 16&, while the lymphocytic depletion types, diffuse fibrosis and reticular, include 68 cases or 18&. The mixed type, intermediate between the extremes, comprises 97 cases or 26%. When we consider the survival data, it is apparent that there is a significant relation between histologic types and median survival. There is a striking difference in median survival between the L & H types with lymphocytic proliferation with 12.4 and 7.4 years, as compared to the lymphocytic depletion types, diffuse fibrosis and reticular, with 0.9 and 2.3 years respectively. The median survival in nodular sclerosis is also significantly longer than mixed, diffuse fibrosis and reticular types.

It is particularly significant to note when consiedring survivors that 23 of the 56 or 41% were classified histologically as nodular sclerosis which would be included in the granuloma type of Jackson and Parker. Twenty-one survivors were found in the L & H gorups.

COMPARISON OF HISTOLOGIC CLASSIFICATIONS

(Next Slide) The classifications of Jackson and Parker and the authors are related schematically in this Table. It his apparent that the granuloma type of Jackson and Parker incorporates most of the histologic expressions of Hodgkin's disease and includes nodular sclerosis, mixed and diffuse fibrosis types and the L & H types, both nodular or diffuse where histiocytes predominate, and all of the reticular type except the small proportion of cases with a predominance of pleomorphic Reed-Sternberg cells or the sarcoma type.

(Next Slide) Comparative classifications of the 377 cases in our recent study according to the criteria of Jackson and Parker resulted in 30 cases (8%) being classified as paragranuloma, 344 cases (91%) as granuloma and 3 cases (1%) as sarcoma. This represents a distribution similar to that reported in the majority of studies. It is apparent that the granuloma type is a heterogeneous group, encompasses a variety of histologic expressions and includes the overwhelming majority (91%) of the cases of this series.

The prolonged median survival of 11.2 years with paragranuloma and the exceedingly short median survival of 0.6 years with sarcoma are significant, but the groups are small.

The prognostic value of the classification of Jackson and Parker is limited to the paragranuloma group which included only 12 (21%) of the 56 survivors; the remaining 44 (79%) survivors at 15 years exhibited features of granuloma. This finding represents dramatic evidence of the limitations of the classification of Jackson and Parker in prognosis.

(Next Slide) By comparison the histologic classification with our types 44 survivors (79%) are placed in the prognostically favorable histologic groups the L & H types and nodular sclerosis. The relationship of these histologic types to clinical stages is believed to be further indication of their prognostic value.

GROSS PATHOLOGY

A few brief comments on the pathology of lymph nodes and the distribution of lymph node and organ involvement in Hodgkin's disease are belived indicated, particularly where a relationship to the histologic findings appears to exist. In the lymph node exihibiting lymphocytic and histiocytic proliferation (L & H types) evidence of lymph node involvement is generally confined to a single large node or a cluster of enlarged nodes, most commonly in the cervical region. The individual nodes may vary 3 — 5 cm. in diameter, but excision biopsy appears to be the limiting factor for the size of the nodes. The lymph nodes are well defined, nonadherent, soft to moderately firm, and have bulging moist tan to grayish-white cut surfaces.

(Next Slide) In the nodular sclreosing type, lymph node involvement appears to be limited primarily ot an inverted triangular region that includes the anterior superior mediastinum, the scalene, supraclavicular and lower cervical regions. In our series, the nodular sclerosing type at the time of initial involvement was associated with an incidence of mediastinal involvement 15 times as great in Stage I as in all other types combined and more than twice as frequently when all stages are combined. The nodes may vary extensively, depending upon the degree of collagen formation and, apparently, on the occasional nonfiltrative character of the celular prolifeartion. The lesion usually consists of a well-defnied firm to hard individual lymph node or densely clusteder matted nodes forming a single well-defined large mass.

(Next Slide) In the mediastinum it may resemble a thymona radiologically except that it is usually located high in the anterior superior mediastinum.

(Next Slide) The cut surface typically exhibits a distinctly nodular character, with firm dense retracted grayish-white niterconnecting bands, circumscribing slightly bulging yellowsh-tan areas that may exceed 1.0 cm. in diameter. On a few occasions ni our experience the mediastinal masses removed surgically have involved the thymus partially, even though Marshall has shown that thymic involvement in Hodgkin's disease is distinctly unusual in autopsy material. At times in the nodular sclerosing type the lesion may be ill defined, with infiltration of adjacent tissue and organs, and absence of discernible lymph nodal demarcation. The cut surface of these lesions may contain areas of dense, retracter, grayish-white tissue, inetrmingled with firm grayish-withe, so-called "fish flesh" — appearing, tissue.

(Next Slide) The classical gross appearance of the lymph nodes in Hodgkin's disease is found in the remaining histologic types, the mixed, diffuse fibrosis, and reticular.

(Next Slide) When observed at autopsy they may form continuous, adherent, irregularly nodular masses that follow the major vessels in the abdomen, encompass the aorta and vena cava and even the adjacent ureters, and extend from the inguinal ligament to the diaphagm. The involvement provides the morphologic counterpart of the remarkable process recently observed by lymphangiography. Similar massive contiguous involvement may be observed in the thorax extending from the diaphragm to and above the clavicles, about the great vessels, into the hilus of the lungs, over and through the pericardium.

Pathologic evidence of the extent of lymph node involvement is available essen-

tially only in autopsy material in which there usually has been extensive modification by a variety of therapeutic agents. The occurrence of continuous masses of lymph nodes at this time does provide support for the belief that Hodgkin's disease may disseminate by direct extension. This evidence, however, is of limited reliability since it is derived from extensively modified advanced disease.

(Next Slide) The nodular character of the involvement of the spleen, liver, and bone marrow, represents a type of involvement that is similar to that observed with metastatic tumors or disseminated granulomas. Isolated nodules of varying frequency are irregularly distributed throughout these tissues. The predominant histologic character of these disseminated nodules is of the diffuse fibrosis or reticular type with the former usually predominating.

Extensive infiltration of organs and extra lymph node tissue, such as the adrenal in retroperitoneal infiltration, may occur, with obliteration of architectural features of the involved organ. Histologically they are usually either the diffuse fibrosis or reticular types, and at times both may be seen in different portions of the process in association with varying degree of pleomorphic changes in the reticulum cells. This infiltrative aggressive form of Hodgjin's disease has been used as evidence for the neoplastic character of Hodgkin's disease.

DISCUSSION

The numerous histologic expressions found in Hodgkin's disease appear to represent manifestations of differences in the host's response rather than a mixed lymphoma as suggested by Lumb and Berman. Evidence of the importance of the lymphocyte in the response of the host is provided by the association of lymphocytic proliferation of the L & H types with clinical Stage I and prolonged median survival, and of the lyphocytic depletion types, diffuse fibrosis and reticular, with Stage III and rapidly progressive disease. The role of the lymphocyte in Hodgkin's disease appears to be related to the recently observed immunologic defect that is manifested by an inability to develop delayed bypersensitivity, delay in homograft rejection, and the depletion in lymphocytes in the inflammatory reactions in the skin window of Rebuck. Support for a lymphocyte defect is becoming apparent also in the form of defective lymphocyte transformation with phytohemagglutinin in the studies of Hirschhorn et al., Aisenber, and R. J. Lukes, J. W. Parker, and H. Wakasa (in preparation). The inverse relationship of lymphocytes and Reed-Sternberg cells observed by Rosenthal and the authors is a dramatic demonstration of the interplay of the host factors and the basic alteration of the disease as manifested by the Reed-Sternber cell. From my experience with histologic material from over 3000 cases, the basic process seems to involve the Reed-Sternberg cell, while the associated cellular and connective tissue features represnet expression of the attempted response of the host.

The association of a variety of inflammatory type cellular proliferations with Red-Sternberg cells raises a serious question about the neoplastic nature of the process. The variation in the character and frequency of Reed-Sternberg cells in the various histologic types provides the basis for the proposal that the Hodgkin's disease process may represent the gradual induction and development of malignante neoplasia and that the numerous histologic types reflect differences in the effectiveness of the host's ability ot prevent the neoplastic induction. If this proposal is correct, fully developed neoplasia may be limited to the small proportion of cases in the reticular group with definite pleomorphism.

Classification of Hodgkin's disease as a neoplasm is based on the generally progressive character of the process, the occasional pleomorphic appearance of the Reed-Sternberg cell, and the tumor-like disseminated masses observed at autopsy that may exhibit infiltrative features. The indistinguishable appearance at times of the histologic findings of the fulminating terminal phase of Hodgkin's disease with those of histiocytic lymphoma (reticulum cell sarcoma) has been used as further suppor for the neoplastic nature of the process. The critical point appears to revolve about the debatable issue whether the Reed-Sternberg cell is a neoplastic cell or simply a modified reticulum cell that at times may become

pleomorphic — at which time it is definitely neoplastic. The common occurrence of numerous abnormal reticulum cells, without the distinctive features of classical Reed-Sternberg cells, that appear to represent intermediate or partially developed Reed-Sternberg cells provides support for the latter possibility. It has not been established whether the process, if neoplastic, involves all the cellular components and is a mixed lymphoma as proposed by Lumb, Berman and others, or the **(Next Slide)** Reed-Sternberg cell is the only neoplastic component — if indeed it is a neoplastic cell — and the associated histologic components are inflammatory reactions. Definite evidence of neoplasia is observed as a sarcomatous type in a small proportion of cases at biopsy with fulminating disease and a limited number of cases at autopsy where Reed-Sternberg cells predominate and are distinctly pleomorphic. Biopsy specimens in the majority of cases exhibit morphologic expressions of an inflammatory process associated with an increase in the frequency of the Reed-Sternberg cells and a decrease in lymphocytes and other cellular elements with progressive disease. The change in character of the Reed-Sternberg cells with the development of distinctive pleomorphic features provides a basis for suggesting that evolution of the Hodgkin's disease process may represent the induction of malignant neoplasia. In this situation the cellular and connective tissue components associated with the Reed-Sternberg cells would represent expressions of the host's attempt to counteract the induction of neoplasia. This consideration fits well with the associated variable cellular proliefration and the inverse relationship between lymphocytes and Reed-Sternberg cells. The possibility to neoplastic induction in Hodgkin's disease is unanswerable at the present time, but require thorough consideration and investigation.

Several types of abnormal reticulum cells that are probably related to Reed-Sternberg cells are observed in association with two of the histologic types tha twill be described in a subsequente section.

(Next Slide) With lymphocytic proliferation where classical Reed-Sternberg cells are infrequent and difficult to find, numerous peculiar and abnormal reticulum cells are found with folded overlapping lobes, with delicate lacy chromatin and small nucleoli. This type appears to represent a partially modified reticulum cell, and possesses the polyploidism, but not the huge nucleoli, of Reed-Sternberg cells. In the nodular sclerosis type, an unusually large abnormal reticulum cell is found, often in great numbers. These cells have abundant pale eosinophilic cytoplasm, at times with an area of condensed deeply eosinophilic cytoplasm, adjacent to the nucleus that has a tendency to be excessively multilobated with many small individual nuclei. Although these distinctive abnormal reticulum cells of nodular sclerosis are generally numerous and exhibit polyploidism, characteristic diagnostic Reed-Sternberg cells with huge nucleoli, vesicular nuclei, and amphophilic cytoplasm are often difficult to find.

In considering the variations of Reed-Sternberg cells and possibly related abnormal reticulum cells it seems that the number and type of Reed-Sternberg cells appear indirectly related to the intensity of lymphocytic proliferation. Where lymphocytic proliferation is prominent, the number of characteristic Reed-Sternberg cells is rare, although the peculiar polyploid reticulum cells with delicate, lacy chromatin may be numerous. Where lymphocytes appear to be depleted, typical Reed-Sternberg cells with characteristic polyploid vesicular nuclei and huge inclusion-like nucleoli are numerous, and at times the pleomorphic type may be evident. The distinctive abnormal reticulum cells associated with lymphocytic proliferation (L & H types) and nodular sclerosis appear to represent modified reticulum cells related to Reed-Sternberg cells, but they are not regarded, however, as diagnostically reliable Reed-Sternber cells.

Establishment of the L & H types permitted the recognition of the prognostic importance of the histiocytic component, which more than doubled the size of this favorable prognostic group with lymphocytic proliferation in our series of cases. The significance of the relationship of lymphocytes and histiocytes is unclear, although the presence of a prominente number of histiocytes seems to indicate a less effective host response. The proposal that lympho-

cytic and histiocytic proliferations should be considered jointly appears justified. This belief is based on the observation that (1) lymphocytes and histiocytes occur consistently together in varying degrees and are difficult to separate; (2) the proliferation of lymphocytes or histiocytes when either predominates may be nodular or diffuse; and (3) the L & H lesion is associated with Stage I disease. Recognition of the diffuse and nodular types of L & H seems clearly indicated from the striking difference in the median survival recorded in Table 4, with 7.4 years for diffuse and 12.4 years for nodular.

Advanced degrees of fibrosis in Hodgkin's disease have been included in the past under the old term, "classical Hodgkin's disease" or in the "granuloma type" of Jackson and Parker. It was emphasized as somewhat distinctive by Smetana and Cohen by the term "granuloma wiht sclerosis," but this term included the two distinctive types of advanced fibrosis idenitfied by the authors, nodular sclerosis and diffuse fibrosis. Through the years the prognostically favorable nodular sclerosis has been combined with the rapidly progressive diffuse fibrosis as a single group of advanced fibrosis and more recently have been included within the granuloma type.

The failure to separate these lesions undoubtedly accounts for the debated significance in the past of advanced fibrosis in Hodgkin's disease. Rosenthal many years ago, however, emphasized the unfavorable nature of fibrosis in his F & R' type, which was never accepted but now appears to be related to diffuse fibrosis. Nodular sclerosis and diffuse fibrosis are readily separable histologically. Nodular sclerosis is identified by the occurrence of birefringent collagen band formation with a tendency to nodule formation and the presence of distinctive large cytoplasmic Reed-Sternberg cells. Diffuse fibrosis exhibits cellular depletion and disorderly nonbirefringent loose hypocellular connective tissue. The distinctive histologic character and prognostic significance of nodular sclerosis has been supported by Hansen. At the recent Paris meeting on Hodgkin's disease, nodular sclerosis emerged as the most significant prognostically of the histologic types in the review (R. J. Lukes, C. C. Nezelof, and C. Gompel, in preparation) of the pretherapy lymph node biopsy material from the prolonged survival cases collected from many of the major radiotherapy seriee of cases Hodgkin's disease.

The mixed type appears to be useful to identify the histologic type intermediate between the lymphocytic and histiocytic proliferations at one extreme and the lymphocytic depletion types, diffuse fibrosis and reticular types, at the other extreme.

The sarcoma type of Jackson and Parker is histologically distinctive, and a separate designation may be justified on this basis. However, the infrequency of this type in biopsy specimens — 1% in our series — and in autopsy material where there is extensive therapeutic madification, provided sufficient evidence for the authors to include the lesion in the reticular group. Furthermore, the remaining cases of the reticular group appears in general to present a relatively similar rate of progression, particularly in Stage III disease.

RELATIONSHIP OF HISTOLOGIC FINDING TO CLINICAL STAGES IN HODGKIN'S DISEASE

DR. ROBERT J. LUKES

INTRODUCTION

The significance of the wide variation in histologic features in Hodgkin's disease has perplexed pathologists since the initial microscopic studies of Greenfield in 1878 and provided the basis for the still existent controversy over the precise nature of the disease. Clinicians have been similary puzzled by the different clinical forms varying from a fulminating febrile form of a few months' duration to a prolonged asymptomatic course of 15 or more years.

A direct relationship between survival and lymphocytic proliferation associated with infrequency of abnormal reticulum cells was reported first by Rosenthal. The description of the paragranuloma type of Hodgkin's disease by Jackson and Parker, however, represented the initial association of histologic features wich localized disease manifestations and slowly progressive disease. This association has been supported by Harrison in a study of prolonged survivors and also by Wright. The distinctive histologic character of this lymphocytic proliferation, however, was sufficient for Smetana and Cohen and Bonenfant to question its relationship to Hodgkin's disease and stimulate Robb-Smith to propose the term "lymphoreticular medullary reticulosis" and Lumb "reticular lymphoma" for this lesion. The sarcomatous type of Jackson and Parker relates a predominant proliferation of neoplastic reticulum cells of the Reed-Sternberg type with rapidly progressive disease. Winterhalter as well as Cro'zat et al, however, were unable to find definite evidence of a relationship between the histologic features and the course of Hodgkin's disease. The widely used classification into paragranuloma, granuloma, and sarcoma proposed by Jackson and Parker appears to have gained only limited support. The infrequency of paragranuloma and sarcoma has resulted in the inclusion of the great majority of all cases in granuloma and limited the prognostic value of the classification.

The application of a clinical staging method by Peters to survival studies in Hodgkin's disease and in the evaluation of the effectiveness of radiation therapy without regard to histologic classification presented a new analytic approach. The extent of involvement when therapy was instituted was

regarded by Dr. Peters as the most important factor in survival. Localized lymphadenopathy, Stage I, was observed with prolonged survival and effective therapy, while generalized involvement, Stage III, was associated with rapidly progressive disease and poor response to therapy. Intensive radiation therapy of the involved lymph nodes and the proximal region was believed to improve the survival rates. The value of clinical staging in survival has been reported by many observers. The subsequent study of Peters and Middlemiss provided further support for the significance of clinical staging and also evidence of the importance of systemic symptoms in staging as a valuable refinement in this approach. A study on the relationship of the histologic changes in involved lymph nodes to the existent clinical stages, however, was never reported until our recent study.

Briefly summarized, our recent investigation in which the significance of the histologic features and clinical stages in survival was evaluated on the basis of 377 U. S. Army cases from World War II (1942-45) appears to have shed some light on the natural history of the disease. The results of this study indicate a relationship between the histologic features, clinical stages, and survival. The histologic types manifested by lymphocytic proliferation were associated with clinical stage I disease and a prolonged median survival; those with lymphocytic depletion were associated with clinical stage III and had a short median survival. An inverse relationship between the frequency of lymphocytes and Reed-Sternberg cells also was noted.

These observations were considered to re-emphasize the importance of the lymphocyte in prognosis in Hodgkin's disease, originally presented by Rosenthal many years ago. They also are believed to be related to the recently described immunologic defect in Hodgkin's disease that is manifested by an inability to develop delayed hypersensitivity and a delay in homograph rejection. The wide variations in the histologic components associated with Reed-Sternberg cells were interpreted as reflections of differences in the state of the host and possibly manifestations of the dramatic interplay in the basic process between the factor(s) involving the Reed-Sternberg cell and the attempted host response. In addition, a new histogic type, nodular sclerosis, emerged with major prognostic significance as a regional expression of Hodgkin's disease in the mediastinum.

In this presentation I will attempt to demonstrate the relationship of the histologic findings and our histologic types, that I have just described, to the clinical stages. This relationship will be interpreted on the basis of our recent study of 377 U. S. Army cases from World War II in a 15 to 18 year follow-up study. Finally, I would like to present a prognostic scheme based on the relationship of clinical stages and histologic types.

This study of 377 U. S. Army cases from 1942-45 is essentially an analysis of Hodgkin's disease in young American males of military age. The group is composed of 370 males (98 per cent) and 7 females (2 per cent). There are 360 Caucasians (95 per cent) and 17 Negroes (5 per cent). The observed ratio of Caucasians to Negroes of 2:1 is based on the 10 per cent Negro incidence in the Army during this period and is similar to that observed by others. The age distribution reflects that of the Army population. There are 282 cases (75 per cent) between the ages of 18 and 30 and only 12 (3 per cent) in the 5th and 6th decades. The distribution of cases according to intervals is the following: 18 to 20 yers, 22 cases (6 per cent); 3rd decade, 260 cases (69 pe rcent); 4th decade, 83 cases (22 per cent); and 12 cases (3 per cent) in the 5th and 6th decades. The median age is 25 years. There is no significant difference in the median age of the patients in the various histologic groups.

Clinical stages to survival: The distribuition of cases into clinical stages according to the original method of Peters is recorded in this table in comparison with the distribution of cases by a modification of the method of Peters and Middlemiss in which stages II and III are subdivided according to the presence or absence of systemic symptoms. There are 142 cases (38 per cent) in stage I, 127 cases (34 per cent) in stage II and 108 cases (28 per cent) in stage III. Since the staging was accom-

plished retrospectively from clinical records without the advantage of lymphangiography, the proportion of cases in stage I is unquestionably larger than if based on a present-day prospective evaluation. The influence of systemic symptoms in staging the same case population results in a meaningful subdivision, particularly when viewed in terms of 5-, 10-, and 15-year survivals.

The influence of clinical stages on survival is summarized in this table. It is readily apparent that there is a definite relationship between clinical stage and survival. The prolonged medial survival of 9.1 years in stage I is in marked contrast with 3.2 and 1.3 years for stages II and III, respectively. From this observation it appears that, in a large number of patients with localized manifestations, the disease remains quiescent for many years. It also indicates, as does the presence of 51 of the 56 survivors at 15 years in Stage I, that, in general, stage I represents a quiescent form of Hodgkin's disease and stages II and III represent progressive disease.

The distribution of survivors at 5, 10, and 15 years according to the initial clinical stages of Peters also is recorded in this table. There is a marked contrast in the incidence of survivors in stage I with those in stages II and III disease survived 10 years and only 4 per cent of stage II and none of stage III survived for 15 years. The incidence of survival for the entire group at 5 years (40 per cent) is the same as that reported by Peters and Middlemiss for the males in their group for the same period.

Further comparison of the incidence at 10 years reveals almost identical results with 22 per cent in our series and 24 per cent for the males in their group. The 2 groups are fairly comparable with the possible exception of age, since our series is composed of 98 per cent males.

Histologic types to clinical stages of Peters: The distribuition of cases in the histologic types according to clinical stages of Dr. Peters, based on her initial method of staging, is presented graphically in this figure. Several significant associations are readily apparent. The cases of the L & H types associated with lymphocytic proliferation are observed primarily in stage I and include 78 per cent of the nodular type and 65 per cent of the diffuse type. By contrast, the histologic types with lymphocytic depletion, diffuse fibrosis (62 per cent) and reticular (43 per cent) types, are observed most commonly in stage III. In addition, over 80 per cent of both types occur with stage II and III disease. Nodular sclerosis and the mixed types are observed with almost equal frequency in the 3 stages, with slight predominance in stages I and II.

It appears from this data that the histologic types associed with lymphocytic and histiologic proliferation and few Reed-Sternberg cells primarily are expressed clinically by localized manifestation or stage I. The histologic types with depletion of lymphocytes and Reed-Sternberg cell proliferation or disorderly fibrosis are associated with disseminated disease, either stage II or III. It appears that nodular sclerosis represents a regional expression of Hodgkin's disease. The observation of nodular sclerosis with almost equal distribution in the 3 stages is interpreted as an indication that nodular sclerosis may be observed in any clinical stage as the disease process generalizes. The mixed type is found also in all stages with almost equal frequency and seems to represent an expression of changing disease since it occupies an intermediate position between lymphocytic proliferation represented by the L & H types and lyphocytic depletion manifested by the diffuse fibrosis and reitcular types.

Histologic types to clinical stages and survival: The distribution of cases accoording to histologic types and clinical stages is summarized in this table along with the median survival. The L & H types, which occur predominantly in stage I, have prolonged survivals of 16 years for the nodular type and 9.5 years for the diffuse. Diffuse fibrosis and reticular, the lymphocytic depletion types that are observed most commonly in stage III, have remarkably beief median survivals of 0.4 and 0.6 years in this stage. In stage II and III the L & H types have prolonged median survivals in comparison to other types in these stages, but the groups are too small for statistical significance.

Nodular sclerosis in stage I is of major prognostic significance, with a median survival of 11 years, since it is by far the most common lesion observer in stage I with 53 cases. By contrast the next most common type in stage I, the mixed type with 36 cases, has a median survival of 4.8 years. Nodular sclerosis and mixed types in stages II and III have fairly similar median survivals that range from 1.2 to 3.2 years, indicative of progressive disease. The median survival in the reticular type in stage I is surprisingly long (5.7 years) but the number of cases is small.

Mediastinal involvement: The incidence of mediastinal involvement in nodular sclerosis is compared in this figure with all other histologic types combined. Nodular sclerosis accounts for 88 of the 149 cases (59 per cent) presenting with mediastinal involvement. The difference in mediastinal involvement is most marked in stage I, where the frequency in nodular sclerosis (45 per cent) is 15 times that in all other stages combined. In stages II and III the frequency of mediastinal involvement in nodular sclerosis is approximately twice that of all other types combined and it is also numerically greater.

These data demonstrate the striking relationship between nodular sclerosis and mediastinal involvement in all stages of the disease. Thus, mediastinal involvement has no particular prognostic connotation in nodular sclerosis but in all other histologic types it is restricted almost exclusively to stages II and III and is associated, therefore, with a less favorable prognosis. The lesion of nodular sclerosis has been observed almost exclusively in the experience of the authors during the past few years in lymph nodes and masses from the mediastinum, particularly the anterior superior mediastinum, and the adjacent scalene, supraclavicular and lower cervical region. This observation on distribution plus the high incidence of initial mediastinal involvement are believed to indicate that nodular sclerosis is a regional expression of Hodgkin's disease.

Nodular sclerosis as a regional expression of Hodgkin's disease in the mediastinum may be seen with any form of Hodgkin's disease. Although it has not been possible thus far to relate the variations in cellular components in nodular sclerosis to the clinical stage, the sclerosis appears to be predominantly lymphocytic in quiescent disease and composed predominantly of Reed-Sternberg cells in progressive disease. The emergence of nodular sclerosis as a lesion of major prognostic significance is evident from this study and has been supported by the observations of Hanson.

The prognostic importance of nodular sclerosis also was dramatically demnostrated in a comparative study of the prolonged survival cases collected from many of the major radiotherapy groups and reviewed histologically by Lukes, Nezelof and Gompel at the Paris meeting on Hodgkin's disease in February 1965. The majority of the 155 validated cases of Hodgkin's disease surviving more than 10 years exhibited the features of nodular sclerosis. Achievement of cure in Hodgkin's disease now appears to be established as a result of this histologic validation.

The high incidence of nodular sclerosis among those proposed cures raises the possibility that the cure of Hodgkin's disease may be accomplished only in a susceptible condition and usually with nodular sclerosis. Futhermore, consideration of the significance of the histologic types, as expressions of the host's responsiveness and their relationship to the clinical stages, suggests that the effectiveness of therapy to a large extent is dependent upon the state of the host. From these observations and the prognostic schema it now appears that achievement of cure in the course of the natural history of the disease may be accomplished only when it is a quiescent state that is expressed histologically by the L & H types or nodular sclerosis and clinically by stage I disease.

The distribution of the histologic types of Jackson and Parker according to the clinical stages of Peters is recorded in this figure. The occurence of 91 per cent of the cases in the heterogeneous granuloma group, almost equally distributed in the stages, essentially obscures any relationship of these histologic types to clinical stages. Paragranuloma occurs principally in stage I, but the group is mall. The general ineffectiveness of the Jackson and Parker

types is dramatically demonstrated in this figure in a comparison of the incidence of survivors at 15 years with clinical stages. The incidence of survivors in the 30 cases of paragranuloma (40 per cent) is remarkably similar to the 142 cases in stage I (36 per cent) but the number of cases in each group is strikingly different.

Further proof of the ineffectiveness of both granuloma and paragranuloma was provided by the histologie evaluation of the prolonged survival cases in the major radiotherapy groups reported at the Paris Meeting on Hodgkin's disease by Lukes, Gompel and Nezelof, where only 7 per cent the cases with 10 years or more survival were paragranuloma and the remainder exhibited the features of granuloma. In a comparative classification study of the same cases by Lukes, Nezelof and Gompel the majority of cases classified as granuloma according to the Jackson and Parker criteria were classified as nodular sclerosis according to the histologic types of the authors. The ineffectiveness of the histologic types of Jackson and Parker in prognosis now seems to be established definitely from these observations.

EVOLUTION OF TH HISTOLOGIC PROCESS

From the observation on the relationship of the histologic features to clniical stages and survival it now appears possible to propose the evolution of the histologic process as summarized in the Table as an expression of the natural history of the disease. In this proposal nodular sclerosis is considered separately since it has been impossible at this time to establish the sequence of events in this lesion. It appears, however, that there is a parallel between the nodular sclerosing process and the evolution of the process involving the remaining types, possibly because nodular sclerosis seems to represent a regional expression of Hodgkin's disease.

Initially in Hodgkin's disease there appears to be a predominant lymphocytic proliferation with a variable histiocytic component that is associated with clinical stage I disease. When the lesion is nodular it is more likely to remain limited in its manifestations whereas the diffuse type at times may also be found in stage II. The addition of other cellular elements such as eosinophils, plasma cells and mature neutrophils and the early development of disordely fibrosis is indicative of the mixed type and heralds the onset of changing disease that is associated with the appearance of stage II and III disease. Subsequently the depletion of cellular components, except for Reed-Sternberg cells, represented by the diffuse fibrosis and reticular types provides evidence of systemic progressive disease of brief duration, or stages III and IV.

A wide variation in the number and character of Reed-Sternberg cells is associated with the histologic types and the evolving histologic process in Hodgkin's disease. Reed-Sternberg cells are infrequent or rare with the lymphocytic proliferation of the L & H types and numerous and even pleomorphic with the lymphocytic depletion types, diffuse fibrosis and reticular. In addition, the peculiar polyploid variants of Reed-Sternberg cells that may be fairly numerous with lymphocytic proliferation and nodular sclerosis but lack the characteristic huge nucleoli, seem to represent partially developed Reed-Sternber cells. These observations on the frequency and character of Reed-Sternberg cells and the general evolution of the process in relationship to the clinical stages, provide the basis for a proposal that the Hodgkin's disease process may represent the attempted induction of neoplasia. The variation in the histologic findings in this situation would represent varying degrees in the effectiveness of the host's attempt to resist neoplastic induction.

Although it is the contention of some observers that the Reed-Sternberg cells from their morphologic character are neoplastic, it is the belief of the authors that only the pleomorphic type may be neoplastic. This view also conflicts with that the Hodgkin's disease process is a mixed lymphoma. From these brief comments on the possible evolution of the Hodgkin's disease process, particularly the relationship of the histologic types to clinical stages, it appears that the possibility of

cure may be largely dependent on the susceptibility of the process to therapy which is reflected by the histologic type.

CONCLUSION

The effectiveness of the proposed histologic classification in prognosis will ultimately be determined by the ease of application and the prognostic usefulness for other workers. These histologic classifications have proven even more effective in our hands as a basis for evaluating the state of the disease and in estimating prognosis during the past few years than in our reported study because of more ideal control over the quality and selection of biopsies. The commonly emphasized variability of the histologic findings in different sites in Hodgkin's disease that has caused considerable debate now can be answered on the basis of the histologic observations of the authors when considered in relationship to the clinical states. Differences in the histologic findings in 2 sites are believed to reflect changing disease which is related to the existence of lymphadenopathy in more than one area, e.g., stage II or stage III disease. Differences in the findings in a snigle lymphnode in stage I also may indicate that the rate of progression and the state of the host are changing. Our experience with biopsies of recurrent lymphadenopathy in a single region in patients with prolonged survival, however, demonstrates a maintenance of histologic types, one case exhibiting the same L & H nodular process in 5 biopsies over a period of 10 years.

The relationship of the histologic findings to the clinical stages re-emphasizes the importance of staging and provides evidence that the clinical stages are dependent on the state of the host, which is reflected by the histologic findings. A question has been raised whether the correlation in our case material between the histologic type and prognosis is not attributable to the correlation of the histologic type and anatomic extent and that therefore the prognosis is related to the anatomic extent. This consideration, in fact, is the crux of our proposal, but with an important basic difference in the interpretation. The histologic changes do appear to be related to the anatomic extent of the disease. It seems to the authors, however, that the anatomic extent and the rate of progression are related to the state of the host, which is reflected by the histologic type. It therefore appears that the anatomic extent or clinical stage is the result of the state of the host and the histologic type rather than the reverse.

Together the histologic types and the clinical stages provides an effective basis for prognosis as demonstrated in the prognostic schema, from the authors' study, particularly when systemic symptoms are used as criteria to modify staging. From this summary it appears that Hodgkin's disease occurs essentially in 2 forms, quiescent and progressive, with intermediate changing disease. Quiescent disease is associated with the histologic expressions of the L & H and nodular sclerosis types with clinical Stage I. Progressive disease is associated with the lymphocytic depletion types, diffuse fibrosis and reitcular, and with Stages II and III and systemic symptoms. Nodular sclerosis may be found in any form as a regional expression of Hodgkin's disease, but it has emerged as a lesion of major prognostic importance in stage I, where it is the most frequent histologic type and has a median survival similar to the L & H types. Consideration of the histologic types as expression of the state of the host and their relationship to the clinical stages provides a basis for suggesting that the effectiveness of threapy and the possibility of cure, therapeutic or spontaneous, may be largely dependent on the state of the host. Undoubtedly the accuracy of prognosis and the evaluation of the status of individual patients will be greatly enhanced by the addition of immunologic studies as another parameter of the prognostic schema. The importance of the lymphocyte in the histologic process of Hodgkin's disease, the recently demonstrated immunologic defect involving the lymphocyte, and the initial observations of defective lymphocyte transformation with phytohemagglutinin emphasize the key role of the lymphocyte in the Hodgkin's disease process and the need for intensive investigation to elucidate the precise nature of the lymphocyte abnormality.

CLINICAL STAGING OF HODGKIN'S DISEASE

ROUND TABLE LUNCHEON

Chairman: **Dr. John E. Ultmann**
Members: **Dr. David A. Karnofsky**
Dr. Henry S. Kaplan
Dr. M. Vera Peters
Dr. Alan C. Aisenberg

1) — **Dr. DAVID A. KARNOFSKY**

In the first slide we show those factors we think are important in the evaluation of the patient's clinical problem. First we take a careful history. We pay particular attention to the question of fever, night sweats, weight loss, itching, complaint of weakness, inability to do the things that the patient previously had done easily, and cough.

When the patient is examined, one pays careful attention to the enlarged nodes, that can be palpated, the size of liver and spleen and the skin lesions. And finally we have a series of laboratory studies that are necessary. The patient has a complete blood count, a serum electrophoresis, the usual kidney and liver function studies. We do not do a bone marrow examination unless the patient has some evidence of immunologic disturbance such as moderate anemia or markedly elevated white count.

In our experience the bone marrow examination in HD is not necessarily difficult to do in the sense that it is hard to obtain material, as Dr. Ultmann suggested, but usually the bone marrow examination is unremarkable. Only when we have some clinical evidence of bone marrow involvement, that we had been able to occasionally get some abnormal bone marrows. We generally do a needle biopsy because one can get some evidence of the architecture of the bone marrow whereas an aspiration may not demonstrate some of the cells an patterns that are seen in the biopsy.

Finally the X-ray examinations are the chest film, PA and lateral, and, as been pointed out by others, if there is any evidence of hilar involvement stereo and tomograms may be indicated. Intravenous pyelogram, along with inferior vena-cavogram, a flat film of the abdomen, abdominal lymphangiogram and a skeletal survey should be obtained.

Occasionally we do immunological studies which Dr. Aisenberg has already discussed.

The bone marrow examination is elective, the tomogram is elective and the inferior vena-cavogram is elective.

In the process of staging it is no longer necessary to obtain a pre-treatment staging, but one should follow patients periodically post-treatment, to get some idea of the rate

* Transcrição da gravação **não revista** pelos autores. Ver págs. 67-70 do Simpósio.

of evolution of the disease, if there is persistent or new disease ocurring, and to get some idea of how effective the treatment was in eliminating the manifestations of the disease.

This demonstrates the follow-up procedures made at one month following treatment: physical examination, symptomatic analysis, blood picture. At two months we get a chest films, a blood count and subsequently, depending on the particular manifestations of the disease and the findings during the preceding tests we will decide about any additional procedures which are indicated.

If these procedures are carried out when the patient is first seen and before any treatment is given we are in a far better position to stage the patient and interpret the results of treatment.

I think it is important to emphasize that staging is not a complete solution to the problem of indicating the activity of the disease. This is a simple short-hand method of communicating with other physicians as to the probable stand of the disease and the evidence of symptoms, that might be related to active HD. But ultimately we try to interpret the activity of the disease, the extent of its response to treatment. It's very important to have a baseline observation before treatment is initiated so that one can know what changes develop as the disease progresses or if the disease remains static we have evidence of no change in these tests.

Staging is not a single, simple concept that has evolved over the last few years. Some time in 1930, or so, Dr. Craver suggested a class of HD, above and below the diaphragm and HD with symptoms. Dr. Easson has proposed a very simple staging of patients with symptoms. It is pretty clear prognostically that patints with symptoms will not do as well as patients whitout symptoms. The subsequent staging methods by Dr. Peters and by Dr. Kaplan as a modification of Dr. Peters' staging have been discussed.

I want to point out that "A" refers to the patient who has no symptoms of generalized disease as interpreted by the clinician, and "B" the patient who has symptoms of generalized disease. If the disease is located in a single area of the body it is stage I. If it is located in two or more proximal lymph node areas it is Stage II. If the disease is above and below the diaphragm, then the patients falls in Stage III. Certain modifications as to whether the disease is extra--nodal or if the disease has been completely eliminated clinically at the biopsy it falls in one of the Stages that Dr. Kaplan has mentioned.

Finally I think it is important to note that as patients are followed these stages are not static, unless the patient is cured. And we have to re-assess the extent of the disease and the patient's problem and in a sense we stage the patient as time goes on.

2) — **Dr. HENRY S. KAPLAN**

The points that Dr. Ultmann and Dr. Karnofsky have already brought up deal actually with the diagnostic evaluation of the patient after a biopsy diagnosis of HD is made. A complete diagnostic work up should be done on every patient in order to stage such patients as accurately as possible, and in order to come to a rational decision about the modality of treatment that is appropriate for each case. These points have been covered adequately and do not require repetition by me. We'd like to stress that we have made quite liberal use of additional biopsies in any situation where the presence of equivocal lymph node disease would have led to a change in the staging of the patient. For example when a lymphangiogram is equivocal as is proved in about 15% of our cases, and where this would make a critical difference in the management of the patient, we have not hesitated to ask our surgeons to do a laparatomy and a biopsy of these specific nodes that are questioned on the lymphangiogram. And usually the surgeons are asked to put a metal clip on the site of the lymph node that is removed so that we can check later on, with an abdominal radiograph to find out whether, in fact, the node that we wanted is the node that was actually removed. Only in this way can one stage with maximal accuracy by present diagnostic techniques. We have found that in some cases tomograms of the lung or of the

mediastinum are helpful in establishing the presence of disease in the mediastinal nodes and in the lungs, and should be used freely in suspected cases.

Lymphangiograms have already been dealt with by Dr. Ultmann. I cannot stress too strongly the importance of lymphangiography and I do want to start out with a couple of slides which indicate, once again, the great importance of lymphangiography in detecting early disease in the abdomem.

Here you see from our first 50 consecutive cases, that Dr. Rosenberg and I studied, that only 5 of the 50 have palpable nodes in the retro-peritoneal area. When they had intra-venous pyelograms, 2 additional cases were seen to show deviation of the ureters When inferior vena-cavograms were done a total of 14 were abnormal, but when lymphangiograms were done it was found that nearly half of the 50 cases had abnormality. Most of these would have been missed by the less specific and less sensitive techniques of palpation, inferior vena-cavograms and intravenous urography.

This is from data of Burton Lee and associates at Memorial Hospital, but here are 46 cases of apparent Stage II disease. Thirty four of these had an I.V.P. (intra--venous pyelogram) and only two of them were positive. Twenty one of them had an inferior vena-cavogram, only 8 of them were positive. Note that 43 had lymphangiograms, and half of them, 22, os 51% were positive. When all of this information was taken together with the original information we find that only 24 cases were still Stage II and half of them, 22 or 51% were positive. Stage III, largely by virtue of the information demonstrated on the lymphangiograms.

I want to stress the great importance of using open, surgical biopsy of the bone marrow, we usually do the iliac crest, or one can use the Vim-Silverman or drill biopsy techniques. The simple aspiration of of bone marrow is essencially useless. You see here in 11 cases out of aproximately 200 in which positive marrows were detected, approximately a 5% incidence of bone marrow involvement case. In only one that happened to have a clot, was there a positive marrow on aspiration. All of the others had both an aspiration and a biopsy and the aspiration was negative in every single case. In these that were positive note the frequency of fever, note the frequency of elevated alkaline phosphatase level in the serum. Most of the patients with an elevated alkaline phosphatase, in this particular group, did not have liver involvement as the explanation of this elevated alkaline phosphatase, and we think the explanation is due to destruction of bone associated with bone marrow infiltration. Many of them, as you can see, were anemic.

In the course of studying our series of cases I think it is fair to say that we have been using lymphangiography routinely, together with bone marrow biopsy and the other procedures, enumerated by Drs. Ultmann and Karnofsky on every single case of previously untreated HD that we have seen for the past 5 years. At the present time I imagine that this is perhaps the largest series, of consecutive cases, in which all patients have been evaluated by this rather extensive diagnostic work-up. Accordingly the data do give us some information which is of interest because in many previous series in which investigators have looked at such data, they have not had the benefit of lymphangiography or bone marrow biopsy.

As might have been predicted the cervical node involvement was the most prevalent finding during the initial work-up of 177 fresh, previously untreated patients. It was positive in 90%. Mediastinal involvement was present in 94% and this is higher than the figure in Dr. Ultmann's series. I think he believed that his were the higher than usual but I think that our series is actually higher than his. Axillary nodes in 36%. Notice that abdominal involvement was as common as axillary involvement. The periaortic nodes were the major site of involvement, spleen less often, liver infrequently on first admission. Nodes in the inguinal and femoral area occurred in 24%. Primary involvement of the lung occurred in 5% and bone marrow involvement in 3% of this particular group of cases.

In the course of studying these patients, Dr. Rosenberg and I have become imppressed by the frequency of certain patterns of dis-

tribution which are more common than others in patients that have involvement of two or more lymp node sites. Thirteen out of the first 100 consecutive patients had involvement in both sides of the neck and the mediastinum. Seven cases had involvement of the left neck only. Five had involvement of the right neck and the mediastinum, and so on. The numerals in each case refer to the number of patients with the particular pattern that is shown.

We have been interested in the fact that so many of them apparently had involvement of contiguous lymph node chains. In these 177 previously untreated cases 22 had only a single site of involvement, 13% of the total series. 119 cases had involvement of two or more sites and were in contiguous sites and only 34 cases, or 19% had involvement of two or more sites and were apparently discontinuous. Of the 34 cases, 14 involved a discontinuous spread to an extra--lymphatic site, such as the lung or the bone marrow. 20 of them evolved a discontinuous involvement within the lymphatic system. Of those 20, which constitute only 11% of the series, 15 of the 20 involved an apparent skip across the mediastinum where we believe that the thoracic duct may be the anatomical connection, still within the lymphatic system, that provides a comunication between the neck and the periaortic lymph nodes. Moreover we have since been able to follow the course of some of these apparent skips across the mediastinum and in the patients who have not been treated to the mediastinum and to demonstrate that in some of them mediastinal disease does later appear, indicating that even some of these are due to the presence of inapparent mediastinal involvement. Wherever the skipped area was the mediastinum and was treated, ons obviously cannot evaluate the later course. But in 5 instances in which the mediastinum was not treated, in 2 there was later involvement of the mediastinum, indicating that these probably were involved from the beginning.

We have also tabulated the next site of involvement, that is of extension of disease in 26 patients in whom later disease appeared, and in 22 of these the next site was in the next contiguous lymp node chain. For example this patient had involvement in both sides of the neck and in the mediastinum. The next area of involvement was in the periaortic chain as shown by the this red area. Two other similar cases are shown here. In other cases the extension was to the iliac or the inguinal areas on both sides, and so on. 22 out of 26 (or 90%) of this series had such contiguous extensions.

The next slide showns the distribution of contiguous and in non-contiguous disease, not only in Hodgkin's disease but as we have seen it, thus far, in the otner types of lymphoma. 89% of our Hodgkin's cases then have had contiguous involvement when they have had two or more sites. 11% have been non-contiguous. One can, therefore, rely on contiguous involvement in HD to a very great extent. Here we have a reticulum-cell sarcoma, still a surprizingly high degree of involvement in contiguous areas. 36 were contiguous, 13 were not. In lymphocytic lymphosarcoma, however, many more patients had discontinuous involvement primarily into the bone marrow. In giant-follicle lymphoma the series is still quite small but most of them are apparently of the contiguous pattern of distribution.

You have seen various stagings. Dr. Ultmann showed you two, one based on Dr. Peters original 3-stage classification, then he showed you one of the earlier ones that was adopted after some additional discussion, Dr. Karnofsky showed you some evolutionary ones. The one we show on this slide is probably not the last one that you will see but it is the last one I think that exists at the moment, and it is the one that was agreed upon at the conference in Rye, New York. I believe that this is the classification that has been translated for you into Portuguese and that was distributed this norning.

The division between Stages III and IV, is preserved in this classification, that is to say, Stage III now refers to involvement of lymph nodes, spleen, Waldeyer's ring, thymus, both above and below the diaphragm in any number of sites, whereas Stage IV is reserved for extension beyond the lymphatic system into any of the structures that you have already heard mentioned. The only difference here between staging

you saw in Dr. Ultmann's slide and this one here is that, in order to achieve some harmony on an international basis, (and this classification has now been proposed by an international Committee, for international adaption), in order to achieve harmony it was necessary to do a little bargainning, and the major bargain that has been done was to modify Stages II and I so that patients not only with one anatomic region, but also patients with two contiguous, (and the important word her is contiguous) anatomic regions of involvement are included in Stage I. Stage II now refers to involvement either in more two regions, above or below the diaphragm, or in two regions which are not contiguous on one side of the diaphragm.

This then is the present staging and one uses "A" or "B" to denote patients without symptoms or with symptoms. The symptoms being fever, night sweats and generalized pruritus.

The next slide shows the stage distribution that we have seen on 100 consecutive untreated patients with HD, utilizing lymphangiography and the other studies mentioned, in every single case. We have applied the new proposed international classification now, for a litle over one year, and we've found it quite satisfactory and reasonably simple to use.

There were 10 patients out of 100 in stage I, sub-1, nome, of them had symptoms. There were 14 in Stage I, sub-2, without symptoms and 3 with symptoms, a total of 17. The combined total in a newer Stage I was 27%. In Stage II, the new Stage II, that is, there were 18 without symptoms and 12 with. Note now that the percentage with systemic symptoms begins to go up as we increase in stage. A total of 33 were in the new Stage III and about half of them now have constitutional symptoms. For the total group 39 out of 100 had constitutional symptoms.

DR. M. VERA PETERS

There is no area in the entire field of malignancies that has caused so much conconfusion in an attempt to classify and to adequately classify such as the lymphomas. One needs to satisfy two main demands: first to present a good distribution of groups of cases according to their prognosis and secondly to present distribution of groups of cases who can be treated in a similar fashion. A classification should be helpful in the management of patients.

I'll show first the survival, 5 to 30 year survival in our experience up to 1955 and this is according to our old classification. You will see that from the standpoint of prognosis it was poor, though it was very helpful from the standpoint of management. Stages I and II-A are too close together. Stage II-B and Stage III are too close together. A four-stage classification is much better from the standpoint of prognosis but the survival curve should have fairly even spaces between them. Although I haven't had a chance to make a diagram of our survival curve according to the re-distribution or of the re-shuffling of the past experience, according to the new classification I think certain changes will take place, chiefly in Stage I and Stage IV.

Stage I curve should go higher after 5 years because Stage I now includes some of the best cases out of Stage II-A, and according to our recent experience 35% in Stage I will be advanced to Stage III. Thus, Stage I is getting rid of its worst cases and acquiring some of the better cases. Stage IV benefits by the re-distribution according to the new stages, because in our past experience we didn't even have a 5 year survival in Stage IV. According to the new classification, which puts all patients who present with extra-nodal disease into Stage IV, some of the early cases with extra-nodal involvement which we would have previously considered Stage I are now Stage IV, and this makes the grouping much better from the standpoint of survival curve, and just as it should be, because Stage IV will look much more like our present Stage III. Stage III will move up to a line somewhere between the bottom line and the line for the total series. No change can be made in the survival curve for the total series. In comparing experiences between centers who have fairly similar experiences with respect to the numbers of early cases and the number of advanced cases, the 5, and 15 year survival rates in the total series comprise the only significant comparison between centers.

Just to illustrate what is going to happen with these survival curves I'd like to show you a table which was made up about 6 months ago and that does not include 40 cases which have been examined since that time.

The re-distribution in Stages I, II-A and III-A is a result of a better assessment, lymphography has advanced. In a more recent reckonning in Stage-I 35% have been advanced to Stages III or IV.

This table is important only to show the comparative values of the various specialized diagnostic procedures which have been added to our assessment of the individual patient with HD. Lymphography certainly leads as a test which is valuable in clarifying the stage, the clinical class of any individual patient.

Liver scanning I have put as a single item but the liver scan always had to be supported by some other indication of liver disease before it was accepted as positive, or sufficiently positive to be certain that that patient should be advanced to Stage IV.

This really shows that at the present time we're in a state of flux. Some centers are using the specialized diagnostic procedures and other centers aren't. There are going to be many differences between centers regardless of the actual stage or actual classifications that are being used in that particular center. Until we get to a place where every one is using a complete assessment for all lymphoma cases, a clinical classification really doesn't mean a great deal, except to the people working in their own centers.

DR. ALAN C. AISENBERG

I cannot think of anything that is less enviable than following Drs. Peters, Kaplan and Karnofsky in a consideration of Staging of HD.

I say this for several reasons. My personal admiration and feeling that they probably have the greatest experience, and their opinion is of greatest consequence in this matter. I also say this by virtue of the fact that their Institutions probably have the most carefully studied cases in the world, managed under the most ideal conditions. Probably there are few other institutions that can present comparable data. And mine, though an Institution with strong qualities of its own, I do not believe that our series of HD patients are as well studied or as carefully managed as theirs. Having indicated our failings, I'll just make a few remarks and following them, obviously I'll end up repeating some of their statements, but perhaps in other terms.

My own simple view of staging is that, at the moment we're trying to say, that there are probably 3 groups of patients with HD. There are what we call Stage I and II and I think that probably we agree that all these patients should be cured. Those we don't cure, we either made a mistake in where we placed them, that is, that there was disease beyond the areas that we thought, or we made a mistake in treatment, we didn't achieve what we should have achieved. Perhaps within this group there are a small group of cases that the usual dosage that even Dr. Kaplan and Peters would recommend, in the 4.000 r range, will not cure the disease.

At the other extreme we have what we separated and called Stage IV. Probably we all agree that, those cases we cannot cure and those patients will die of prognessive H D.

In between we have something that we call Stage III and I think that this is an area in which we are uncertain. The strongest and most positive-feeling of us will say that many of those can be cured, others of us are not certain. This is one of the important areas that will have to be cleared up over the next decade. I know Dr. Kaplan feels that many of these are curable. I hope so. I'm not convinced by presently available data that this is true.

As we see HD in a general hospital (MGH) which does not draw patients with HD from around the country, our distribution of cases is not as good as Dr. Kaplan's or Dr. Peters'. We see many more Stage III and many, many more Stage IV. I have not worked up our data yet. I'm fairly sure from other general hospitals like our own that probably only a third of the cases are

in I and II, and probably the other two thirds are in IV.

I think that we are in a period of transition. This particularly justifies very careful work-up that they are doing in their patients with the disease. I think that they will have to show us the way to future management of this disorder. There may be a time when it will not be necessary to do lymphangiography on all patients with localized. HD. And that we will acquire sufficient experience to know those who need it and those who don't. In the mean time, during this critical phase, it is right not to deny possible cure by virtue of overlooking disease.

I certainly agree that supplementary biopsy is not as formidable as one would think. I'm strongly in favor of it, in this period in which lymphangiography is in a state of some confusion. We should have the equivocal lymphangiograms biopsied. It's for the patients benefit and it is the only way we can know what these things mean.

The literature is becoming filled with innuendos as to what lymphangiograms mean which are not backed up by biopsy clarification. It may even turn out that biopsies may not always clarify the situation.

The goal of the Staging is very clear. At the moment Staging is going through a period of transition, we all have to watch and learn. I know that during the next decade I will be watching and learning from the speakers that preceded me.

CHAIRMAN COMMENTS

Dr. John E. Ultmann

I think we have this afternoon had an opportunity to learn about an approach to the appraisal of the patient with HD, an approach that lends itself to meticulous examination, using history, physical examination, laboratory techniques and specialized techniques in order to assess where each individual patient fits into the experience of any one group of patients and with the use of certain modalities of treatment.

Tomorrow in the afternoon we will add to this, the other factors which are responsible for prognosis, some of which are not staging. I think it is fair to say that the more-time one spends with any one patient, in trying to assess where he stands, the better one will be able to prognosticate for this patient, and the better one will be able to plan a rational approach to treatment.

QUESTIONS AND ANSWERS

Dr. Karnofsky: Dr. Peters raised a very interesting matter of staging patients with positive liver scans. I wanted to know if these patients had liver biopsies that were positive or liver function test in association with liver biopsies.

Dr. Peters: We hope to be able to soon do liver biopsies along with the liver scans. because I think that the information one could gleam would be very important. This program hasn't started yet. Very few of those patients had the support of a liver biopsy but, interestingly enough, the majority of the positive liver scans in HD are of the nodular type rather than the diffuse type. The liver scan had to be very significant to be accepted. We took into consideration also symptoms of the patient which suggested that they had disease beyond Stage I. Two of these patients were actually Stage I and had involvement of upper cervical nodes, and I'll be mentioning them in my talk.

It has been suggested by autopsy series, and I've forgotten from where, that liver involvement has to be pretty gross before the alkaline phosphatase is elevated due to liver disease, because in this series with liver involvement, about one third, or less than a third had an elevated alkaline phosphatase prior to death. Certainly one is assuming a little bit, by using the liver scan alone, but if the liver scan is supported by other evidence of disease, and it can be discovered elsewhere, and if the liver scan is definitely abnormal, we will accept it. We've had the experience of radiating these patients with very abnormal liver scans with no other evidence of disease beyond the presenting site, and observing the patients improve dramatically. I'm really not certain, but we don't accept it as the only factor. **Chairman:** Dr. Kaplan do you have some comments on this question? **Dr. Kaplan:** I think our experience is somewhat on the opposite direction. We've tried liver scans

extensively at first and we were quite disappointed. In the first several cases in which we were able to document liver disease by biopsy, in almost all of them, the alkaline phosphatase, or bromosulphalein test, or both, were abnormal and virtually none of these was there an abnormal scan. We may have given up too soon, but we really just have given up on liver scans for the pupose of detecting liver involvement.

I would like to make a comment that I intended to make earlier and forgot to make. I want to make it clear that even going to a stage IV, we should all be aware of the fact that everytime we create a final stage, it becomes a very heterogeneous collecting point for a miscellany of distributions that we can't fit in any where else. Stage IV is still just that kind of a dumping basket. Stage IV due to bone marrow involvement is not the same disease as Stage IV due to lung involment or to liver involment and so on. And I would simply like to stress the point that Stage IV is not a single entity.

Chairman: I migth make one comment regarding the scan which is often ordered because the liver is enlarged in the first place. We have recently reviewed the significance of hepatomegaly in those patients who have come to autopsy. Very much like the data of Diamond and others, and particularly like the data that have been reported in children with leukemia, one can see apparently a non-specific enlargement of the liver, unrelated to infiltration by HD, in very carefully sectioned livers. The hepatomegaly, itself, undocumented by liver biopsy, becomes of questionable significance.

Furthermore, and this is sheer speculation we are impressed by the number of false positive liver scans. We also began to look with a jaundiced eye at our liver scans.

Question (from the audience) — How many patients were involved in the construction of Dr. Peters survival curves?

Dr. Peters: 354 patients, I believe for the 5-year rate and the total number gradually dwindling to about 23 for the 30-year survival rate.

This round table was tape recorded and this transcription was not revised by the participants (The Editor).

CLINICAL STAGING OF HODGKIN'S DISEASE*

DR. HENRY S. KAPLAN

Every patient with Hodgkin's disease, once the histopathologic diagnosis is established, must have a thorough diagnostic evaluation to identify all sites of involvement. This should include a careful clinical history, with emphasis on the presence of unexplained continuous or intermittent fever, night sweats, and/or generalized pruritus. Fatigue and weight loss are important to document, but are less specific. A meticulous physical examination is essencial, and the presence of palpable lymph nodes in any of the accessible peripheral chains should be recorded and described. Equivocal lymph nodes in sites that would lead to a change in staging should be biopsied to establish clearly whether they are involved or not. Chest roentgenograms will usually reveal mediastinal or hilar adenopathy when present, but tomograms of the lung and mediastinum may be helpful in some cases. Lymphangiography is an indispensable part of the most important single reason for major errors in staging, due to failure to detect intraabdominal disease. The status of the liver should de checked by liver function tests, particularly the serum alklaine phosphatase and bromsulfthalein excretion tests. Where these are abnormal without some other satisfactory explanation, biopsy of the liver, either by the needle technique or my open surgical biopsy, is indicated. Finally, bone marrow biopsy, using the drill, Vim-Silverman, or open surgical techniques, is mandatory. When the diagnostic evaluation omits any of the above procedures, errors in staging and in the selection of proper treatment will inevitably increase significantly.

In a series of patients studied in this manner, we have been able to document the fact that, when multiple lymphatic sites are involved, the involvement is not randomly distributed but is seen to involve **contiguous** chains of lymph nodes in nearly 80 per cent of cases. Moreover, most of the instances in which involvement is noncontiguous can be explained satisfactorily by communication between involved lymphatic sites via the thoracic duct, bypassing the mediastinal and hilar lymph nodes. When such instances are omitted, less than 5 per cent of cases remain to be explained as truly noncontiguous lymphatic involvement. Thus, the sites of involvement or of probable future involvement can be predicted with great accuracy in Hodgkin's disease. This is further documented by our previously published data

* Resumo escrito pelo autor.

(1) on the sites of extension of disease in treated patients; it was observed that in over 90 per cent of instances, the next site of involvement was in a contiguous chain of lymph nodes.

The clinical classification we formerly employed was a modification of Dr. Vera Peters' original three-stage classification. It differed from her classification by subdividing her former Stage III two stages: a new Stage III, pertaining to widespread disease in lymphatic structures, both above and below the diaphragm, but without extralymphatic involvement, and a new Stage IV, reserved for cases with secondary extension to one or more extralymphatic sites such as the bone marrow, liver, lung, gastro-intestinal tract, etc. More recently, as the result of discussions held at the international conferences in Paris and Rye, New Kork, in 1965, a slight modification of our four-stage classification has been proposed for international adoption (2). We have adopted and used this new classification for about one year and have found it to be quite satisfactory. Moreover, our data on the survival of patients with Stage III and Stage IV disease, using this new classification, reveal a distinct difference in prognosis which strongly supports the validity of dividing the former Stage III category into these two new categories.

REFENRENCES

1 — ROSENBERG, S. A., and KAPLAN, H. S. — Evidence for an Orderly Progression in the Spread of Hodgkin's Disease. *Cancer Res.* 26: 1225-1231, 1966.

2 — ROSENBERG, S.A. — Report of the Committee on the Stating of Hodgkin's Disease. *Cancer Res.* 26: 1310, 1966.

ESTADIAMENTO DA DOENÇA DE HODGKIN

Nota do Editor

As seguintes definições de estadiamento foram estabelecidas pela Comissão e aprovadas pelos membros da Conferência. Esta classificação representa uma modificação da de Peters e é muito parecida com a recomendada no Simpósio sôbre Doença de Hodgkin realizado em Paris, França, em fevereiro de 1965. Espera-se seja estudada e aceita para emprego internacional.

Estádio I — Doença limitada a uma única região anatômica ou a duas regiões anatômicas contíguas, do mesmo lado do diafragma.

Estádio II — Doença em mais de duas regiões anatômicas ou em duas regiões não contíguas porém do mesmo lado do diafragma.

Estádio III — Doença em ambos os lados do diagragma, porém não se entendendo além do comprometimento de glânglios linfáticos, baço e / ou do anel de Waldeyer.

Estádio IV — Comprometimento da medula óssea, parênquima pulmonar, pleura, fígado, osso, pele, rins, tubo gastro-intestinal ou qualquer tecido ou órgão além dos gânglios linfáticos, do baço e do anel de Waldeyer.

Todos os estádios serão sub-classificados em **A** ou **B** para indicar a ausência ou a presença, respectivamente, de sintomas sistêmicos. Os seguintes sintomas abaixo relacionados são significativos:

a) — Febre;
b) — Suores noturnos;
c) — Prurido

Alguns centros preferirão continuar considerando pacientes com doença limitada a uma região anatômica. Para os que desejarem fazer tal distinção, é a seguinte a sub divisão do Estádio I:

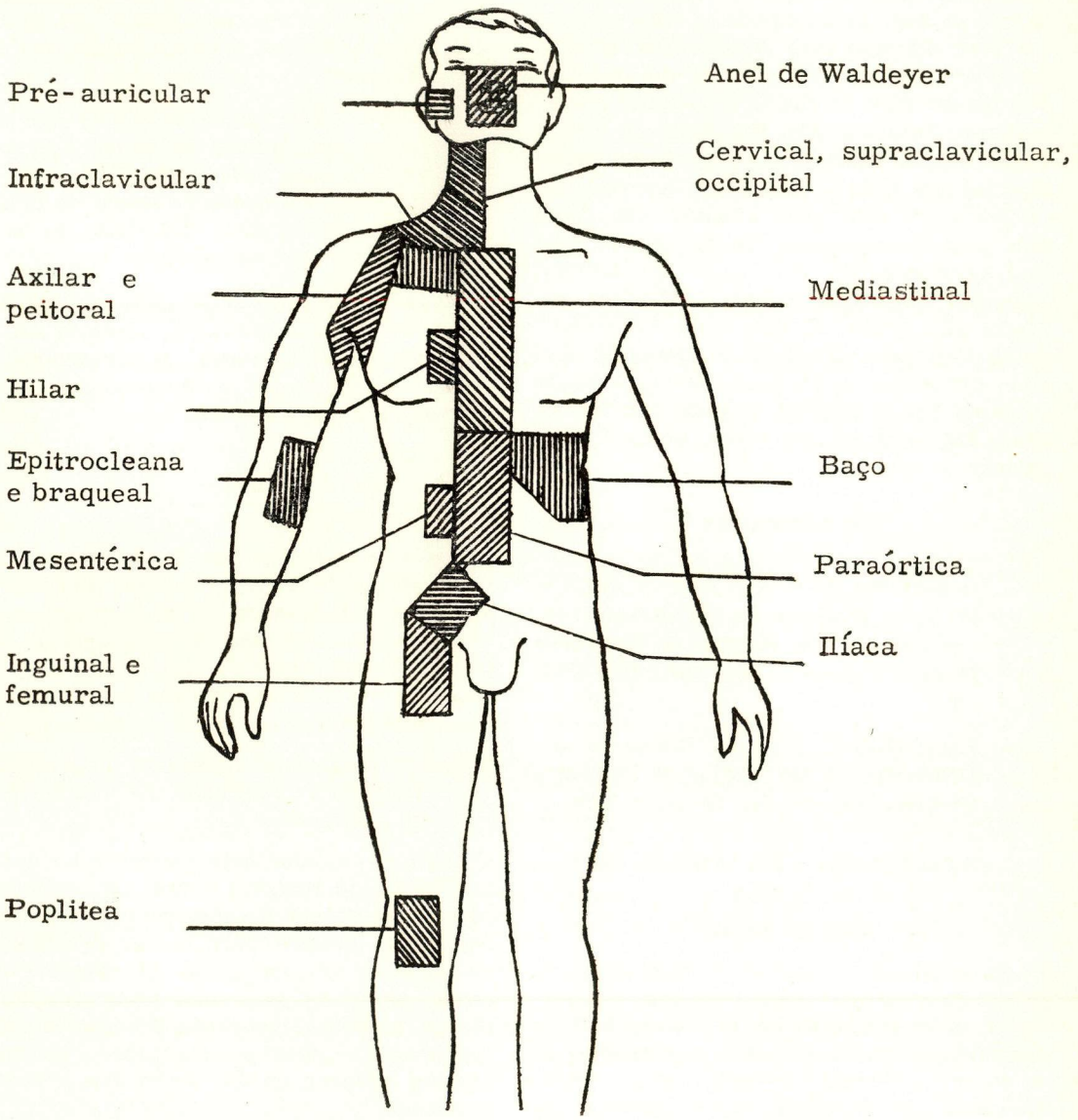
Estádio I^1 — Doença limitada a uma região anatômica.

Estádio I^2 — Doença limitada a duas regiões anatômicas contíguas, no mesmo lado do diafragma.

Outros sintomas que aparecem no curso da Doença de Hodgkin devem ser anotados, porém não devem ser considerados suficientes, por si mesmos, para incluir determinado paciente em sub grupo B. Neste caso estão: perda de peso, mal estar, fraquesa, fadiga, anemia, leucocitose, leucopenia, linfocitopenia, hemo-sedimentação elevada, anergia cutânea, ou dor provocada pelo uso do álcool.

Membros do Comité:
Dr. Maurice Tubiana, Villejuif, Seine, France
Dr.Eric Eeasson, Manchester, England
Dr. Lilian Fuller, Houston, Texas
Dr. David A. Karnofsky, New York
Dr. Robert Lukes, Los Angeles, California
Dr. M. Vera Peters, Toronto, Canada
Dr. Saul A. Rosenberg, Palo Alto, California

REGIÕES ANATÔMICAS A CONSIDERAR NO ESTADIAMENTO DA DOENÇA DE HODGKIN



TREATMENT OF EARLY AND ADVANCED HODGKIN'S DISEASE BY RADIOTHERAPY

DR. HENRY S. KAPLAN

It is imperative that every patient with Hodgkin's disease receive a thorough and meticulous diagnostic evaluation of the extent of the disease in order to provide reliable evidence concerning sites of involvement, both for purposes of staging and for the planning of treatment. The staging classification utilized in the following discussion is the four-stage classification proposed for international adoption at the recent conferences in Paris and in Rye, New York (1).

Treatment with curative intent, for which intensive megavoltage radiotherapy is the treatment of choice, is indicated for all patients with Stage I or Stage II Hodgkin's disease, with or without systemic symptoms, except where such treatment is precluded by the poor general condition of the patient or by extensive previous treatment.A study is currently in progress to establish whether intensive radiotherapy with curative intent is also indicated for patients with Stage III Hodgkin's disease and for selected patients with certain variants of Stage IV disease. For the remaining patients with Stage IV disease, palliative therapy is indicated, an will be described separately by Dr. Vera Peters and others.

Tumor Dose for Intensive Radiotherapy of Hodgkin's Disease. Recent studies (2) indicate that the recurrence rate per treated field decreases rapidly with increasing dose, reaching a minimum at about 4.000 rads, delivered in approximately four weeks, at which dose level the recurrence rate is only about 2 to 4 per cent. This dose is therefore taken as a good estimate of the tumoricidal dose for Hodgkin's disease.

Field Size and Shape. Microscopic disease is often present in other nodes in a chain in which one or two nodes are palpable. Accordingly, it is important to treat lymph node chains in their entirety and to treat contiguous lymph node chains with uninterrupted, shaped fields. A "mantle" technique (3) has been devised for megavoltage radiotherapy of the cervical, supraclavicular, infraclavicular, axillary, mediastinal, and hilar lymph node chains in continuity bilaterally in single shaped anterior and posterior parallel opposed fields. Lead blocks are shaped to the individual contours of each patient, to provide adequate protection for the lung fields, the cervical spinal cord, and the larynx. An optical technique for defining the contours of the lead protective blocks for both lungs

* Resumo da apresentação, escrito pelo autor.

has recently been described in detail by my colleagues, Earle and Bagshaw (4). This technique is so simple that it permits the ready modification of the lead blocks from time to time in the management of patients with massive initial mediastinal involvement. In such instances, it is desirable to deliver only a small fraction of the total dose, usually 1,000 to 1,500 rads, to a very wide field, sometimes including the entire lung. Treatment is then interrupted for one to two weeks or occasionally longer to permit the mediastinal mass to regress maximally. Lung shields can then be introduced, and treatment resumed and carried to a total of 4,000 rads. It is good practice to include the entire cardiac contour in the initial field in order to eradicate possible pericardial extensions of disease. However, the field size should be reduced after the first 1,500 to 2,000 rads have been delivered so that the entire cardiac volume does not receive the full dose of 4,000 rads. With the optical technique, such changes in the shaping of irregular fields with megavoltage are readily accomplished.

Although the mantle technique was originally developed for use with a 6 MeV linear accelerator, slight modifications of the technique make it readily adaptable to telecobalt apparatus and other megavoltage equipment. A treatment distance of 100 cm is adequate for most womem and children, but men, particularly those of large dimensions, may require treatment at a longer distance (130 cm with our 6 MeV linear accelerator). It is imperative that megavoltage energies be utilized for treatment with curative intent, since comparable doses to fields of this magnitude with conventional kilovoltage X rays would yield intolerably severe skin reactions.

In the abdomen, megavoltage beams of rectangular or truncated pyramidal shape are arranged to cover the paraaortic lymph node distribution, taking care to minimize irradiation to the kidneys. A triangular extension at the left upper aspect of the field covers the splenic region. In the pelvis, the iliac, inguinal, and femoral chains may readily be treated in continuity with an inverted Y-shaped field. The persistent opacification of lymph nodes after lymphangiography greatly facilitates the accurate delineation of adbominal and pelvic fields, making it possible to minimize bone marrow and parenchymal damage, while providing appropriate field distributions for the lymph node chains themselves

Tolerance. Extended-field megavoltage radiotherapy to doses of 4,000 rads is remarkably well tolerated. Cutaneous reactions are minimal or absent, and the subsequent cosmetic results are invariably excellent. Mild to moderate pharyngitis or esophagitis is occasionally seen, but disappears soon after completion of treatment to the abdominal or pelvic fields, usually with prompt relief by appropriate medication. Paramediastinal pneumoniits is seen radiographically in about one half of the patients, but only about one third have any symptoms, usually limited to a mild, dry, irritative cough and occasionally slight shortness of breath, which is self-limited in nature. Tolerance of the bone marrow to these extended fields of treatment is also remarkably good, with white blood counts usually remainig above 2,000 and platelet counts above 50,000-100,000 throughout the entire course of treatment.

End Results. Long-term end results by stage will be presented. With optimal technique, about 80 per cent of all Stage I and Stage II cases, including those with constitutional symptoms, can be offered apparently permanent cure (5). Moreover, on the basis of four-year follow up data, it would appear that control of Stage III disease by intensive megavoltage radiotherapy can also be achieved. Our current data suggest that about two thirds of Stage III-A and one third of Stage III-B cases will remain free of disease (6). It is therefore concluded that modern techniques of intensive extended-field megavoltage radiotherapy constitute the treatment of choice for Stages I and II and possibly also for Stages III Hodgkin's disease.

REFERENCES

1 — ROSENBERG, S. A. — Report of the Committee on the Staging of Hodgkin's Disease. *Cancer Res. 26*: 1310, 1966.

2 — KAPLAN, H. S. — Evidence for a Tumoricidal Dose Level in the Radiotherapy of Hodgkin's Disease. *Cancer Res. 26*: 1221-1224, 1966.

3 — KAPLAN, H. S. — Radical Radiotherapy of Regionally Localized Hodgkin's Disease. *Radiology 78*: 553-561, 1962.

4 — EARLE, J. D., and BAGSHAW, M. A. — A Rapid Optical Method for Preparation of Complex Field Shapes. Presented at the annual meeting of the Radiological Society of North America, Chicago, Illinois, November, 1966. Submitted for publication in *Radiology*.

5 — KAPLAN, H. S. — Long-term Results of Palliative and Radical Radiotherapy of Hodgkin's Disease. *Cancer Res. 26*: 1250-1252, 1966.

6 — KAPLAN, H. S., and ROSENBERG, S. A. — Extended-field Radical Radiotherapy in Advanced Hodgkin's Disease: Short-term Results of 2 Randomized Clinical Trials. *Cancer Res. 26*: 1268-1276, 1966.

FACTORS INFLUENCING PROGNOSIS OF HODGKIN'S DISEASE*

ROUND TABLE LUNCHEON
Chairman: **Dr. Vera M. Peters**
Members: **Dr. Alan C. Aisenberg**
Dr. David A. Karnofsky
Dr. John E. Ultmann

Dr. ALAN C. AISENBERG

The prognosis comes after having seen the patient, having had him hopefully treated by the optimal method of therapy, having seen his response to therapy, having seen the absence or presence of recurrence.

As periods go by without recurrence the prognosis improves. As Dr. Peters has pointed out, recurrence in the first year is not that serious a problem; this may not be equally valid when we're talking about recurrence after radical radiotherapy. This recurrence may be seen after somewhat sub-radical radiotherapy. Perhaps these things which evolved in a certain stage of our knowledge will not be true in a later stage.

Prognosis in HD has been one of the traditionally difficult problems in the study of the disorder and the older litterature is filled with statements of how impossible it is to prognosticate HD. I think as the result of work of Dr. Peters and of others certainly one can make some shrewd guesses as to what is going to happen to the patient.

I think in Hodgkin's disease it's a particularly important group of patients for whom one has to prognosticate. Frequently these are young active people trying to plan for their life and one is repeatedly asked what sort of outlook there is. Adding all the simple clinical parameters, the more refined laboratory parameters of lymphangiography, X-ray diagnosis, the added insight that comes from histological studies, one can make a fairly good guess as to what is going to happen.

Given another year to see how things go and what the response to treatment is, I think one's prognosis can be even more accurate. The older statements are no longer true. We can say something of how things are going to go with a certain degree of accuracy.

Dr. JOHN E. ULTMANN, M.D.

Prognosis has always been difficult, as the clinical course of Hodgkin's disease is characterized by great variability. As has been mentioned, progression occurs by successive exacerbations which may appear at intervals of weeks, months, or years. Shimkin, as well as Osgood, have stressed the difficulty of comparing the results of treatment of Hodgkin's disease between

---

* Transcrição da gravação não revista pelos autores.

various centers. This occurs because of differing methods of reporting survival, variability of patient material, and differences in approach to patients over periods of years; yet all patients may be included in a single series from one institution. My favorite view of statistics is the following: "Statistics may be likened to Bikini bathing suits — what they reveal is enticing, but what they conceal is vital." Of all the statistical approaches, the actuarial or life-table method measuring survival from date of biopsy probably reflects results most accurately.

A comparison of a selected number of recent reports shows a 5-year survival for all patients with Hodgkin's disease of 22 to 38% and a 10-year survival of 5 to 24%. The effect on survival of the age of the patients at the time of biopsy is shown on the next slide. It can be seen that the disease progresses more rapidly in the older patients The next slide indicates the effect on survival of sex of the patient; the course of the disease is generally slower in the female compared to males. The next slide shows similar findings in the accumulated studies of a number of other authors.

The effect on survival of duration of signs and symptoms **before** diagnosis is made is extremely difficult to evaluate. The data of Peters and those accumulated in our own institute, however, appear to indicate that the longer the prediagnostic history, the better the prognosis. Presumably, this occurs because the disease is evolving more slowly. Unfortunately, although the exact location of presenting lymph nodes has a bearing on the ultimate survival, this is difficult to evaluate as most series fail to specify the exact location of the lymph nodes beyond the general region, i.e., cervical, supraclavicular, axillary, etc.

The next table summarizes three large series to indicate that according to the Jackson and Parker classification (paragranuloma, granuloma, and sarcoma) there appeared to be a distinct difference in survival between the patients with granuloma compared to those with paragranuloma with a longer survival time and those with sarcoma with a shorter survival time. In our own series, these findings are substantiated. The new histologic classification of Lukes has given a further more meaningful prognostic parameter, particularly in patients with Hodkin's disease beyond Stage I; it has already been discussed by him.

It may be of interest at this time to examine the effect on survival statistics of **reclassification** according to region. On one portion of the next slide is shown the 5-year survival in patients classified according to the old technique. Of the patients with local and regional disease, 37% survived 5 years; of the large group of patients with Stage III, only 20% survived 5 years. When these same cases are reclassified using the new American Cancer Society classification previously discussed, a number of patients previously staged as III become Stage II. These 51 patients, all of whom are classified as I or II pre-lymphangiography, have a 5-year survival of 45%. Of fifty-two patients culled from old Stage III with organ involvement other than lymph node and spleen and now classed as IV only 8% survived 5 years. The 38 Stage III patients who remained had a 5-year survival of 33%. It appears important to re-examine a number of other series in the light of the new staging classification in order to evaluate better the effect of current treatment methods on survival.

The next slide indicates the effect on survival of whether the patient did or did not have symptoms at the time of biopsy. The nonsymptomatic patients, particularly in old Stages I and II, have a significantly better survival than those patient who are symptomatic. Cohen, Smetana, and Miller have attempted to prognosticate regarding survival in the presence and absence of certain clinical and laboratory findings. Using an analogous approach, we have calculated survival from date of biopsy in symptomatic Satge III (Peters) patients with hepatomegaly, i.e., Stage IV (Kaplan). The poor prognosis of a finding of hepatomegaly is a striking finding; it must be emphasized that this refers to liver enlargement only, the presence or absence of actual involvement of the liver by Hodgkin's disease not necessarily having been proven in each one of these patients.

Unlike reports presented in the literature, examination of our patient material indicates that evidence of bone involvement by Hodgkin's disease is an ominous

sign. Patients who had bone involvement at the time of the diagnosis of the Hodgkin's disease (Stage IV) had a short survival. Of those who developed bone lesions later — often patients who had lived for some time with Hodgkin's disease (average 35 months) — one-half died within six months following the onset of this complication.

We have already mentioned the effect on survival of the completeness and the duration of response to the initial therapeutic procedure. This refers, of course in particular, to the radiotherapy given initially. We have been able to demonstrate that the survival from date of the first chemotherapy, however, can also be related to the quality of response to this **first** chemotherapy. Thus, the patients who had a good response to the initial chemotherapy lived considerably longer than those patients who failed to respond to the initial chemotherapeutic intervention.

When one examines the characteristics of the long-term and short-term survivors, it is apparent that no specific feature completely characterizes one or the other group. However, as Karnofsky has shown, the following factors appear to be favourable: female, young adult, outdoor occupation, normal blood count, a long history of localized disease, localization being to one side of the neck and particularly not at the base, weight gain after the first course of treatment, and being asymptomatic. In contrast the unfavourable factors are: male, elderly, abnormal or depressed blood count, rapid progression of disease, generalized disease (in particular, abdominal presentation), weight loss, symptomatic with fever, itching, anorexia, and weakness and signs of splenomegaly or involvement of extranodal sites.

Dr. DAVID A. KARNOFSKY:

We have tried to list, without waiting, the significance of the prognostic factors and many of these are impressions. Some of them are statistically valid. The impressions were told by Dr. Lloyd Craver. Dr. Craver noted that people who were farmers and outdoor people would do better than city dwellers. The blood picture is of significance. If the hemoglobin and the white count are normal when the diagnosis is made, this is favorable.

A long history of a localized lymph node in the cervical area and not in the sub-clavicular area is a further favourable prognosis.

If the patient is asymptomatic when he presents, and if after treatment of any kind, to control the local disease there is general improvement, and gain of weight, this is favourable. In contrast we have the reverse of this. A male in the older age group who comes in with a abnormal blood picture, who has evidence of generalized disease with systemic symptoms, weight loss, has extra-nodal involvement, has an unfavourable prognosis.

It is conceivable that if one were in a position to analyze a large number of cases, and do what Dr. Ultmann did, try to weigh the significance of various factors we may end up with answers which would almost give us a prognosis, adding here, of course, the staging and the histological diagnosis.

There is another factor I think may be presumptuous to comment on but I think it is important and that is that, all things being equal, another favourable prognostic factor, is the presence of a good physician.

If we assume that HD can be better controlled and can be sometimes cured, and life prolonged by adequate treatment, it stands to reason that the patient who is diagnosed and seen by a physician who understands the disease and its manifestation who will plan a course of treatment appropriate to the patient's illness, that this can be an important prognostic factor.

In the US it's been clear that many physicians have undertaken the treatment of HD with inadequate X-ray therapy, or episodic chemotherapy without understanding of the disease or the methods of treatment that have been used. And this is generally the case. It's only in recent years that there has been the opportunity to treat these patients in a planned manner, in terms of determining the nature and the extent of the disease and then finding a treatment.

The second factor besides the presence of a competent, trained physician in this area is the availability of adequate facilities. And this I regard as another important prognostic factor.

It takes radiotherapy facilities to treat HD. Patients treated adequately with low-

-voltage equipment may get into serious trouble from the consequences of radiotherapy. This is another factor in the prognosis in these patients.

Finally I wish to comment on some data. We analyzed 50 patients who have survived more than 10 years. We tried to stage these patients in relation to survival, with and without recurrence. We did not have lymphangiography on these patients and this represents a staging that was made after the fact, that is a retrospective staging.

In 13 patients had with Stage-I disease in the neck and 2 in the groin. Of 15 patients, 12 were males and eleven females. These patients all received some kind of radiotherapy. Eleven at the end of 10 years had had no recurrence, and 4 were alive with evidence of recurrent disease.

The patients that presented with Stage--II-A disease, without symptoms, presented with disease in these areas: 22 in the left neck and axilla, 6 in the right neck and axillae, 1 in the groin. Nine of 14 patients that were Stage- II-A were alive at the end of 10 years without recurrence. In other words of those patients with symptoms, only 3 out of 15 surviving to 10 years had no evidence of recurrence. And this is the list of symptoms: fever, night sweats, pruritus and weight loss.

In the Stage-III patients, only 1 out of 2 patients with II-A disease, and none out of the III-A patients were alive at the end of 10 years, in this series, and one of the 4 III-B patients was alive, but this is an extraordinary patient who apparently had progressive widespread disease, developed measles and went into spontaneous remission and remains well, some 12 years after the diagnosis.

So this emphasizes, in a retrospective study, that the favourable patients, in terms of survival of 10 years after treatment, without evidence of recurrence are in the I and II-A group.

DR. VERA PETERS:

Thank you, members of the panel. I think to summarize we could still cling, from a clinical standpoint, to the clinical classification, regardless of the clinical classification. Dr. Aisenberg pointed out, it's very difficult to define the prognosis when one first examines the patient. Each patient has his own little set of alarm signals. One should listen to the patient, because the patient often can recognize recurrences before we can recognize them.

Dr. Aisenberg also pointed out that the patient's response to the first effort in treatment often gives a clue. This is so right.

The patients tolerance to either radiation therapy or chemotherapy vary. Some patients cannot tolerate radiation therapy and yet can tolerate chemotherapy and vice-versa.

The length of remission after the first attempt to cure, in the early stages is certainly a good indication of the prognosis but that doesn't help one when one is first faced with a new patient.

The histological differences which have been reviewed by Dr. Lukes are most important and next to the clinical extent of disease, next to the clinical staging I believe that histological classification is, probably, the most important.

Dr. Ultmann brought up the significanec of bone involvement and I'll have to review my figures, but after studying this in Stage-IV, I was still under the impression that, generally speaking, the patients with bone involvement did better than the patients with involvement of other extranodal tissues, but I'll have to check on this again and make certain that I am correct. I do agree with him that hepatomegaly, regardless of the reason for it, is definitely a poor prognostic sign. And this is the reason why we are so interested in doing liver scans on all patients, regardless of the stage, on first admission, and reviewing them, again perhaps at six monthly or yearly interval. For a long time we have felt that liver involvement is probably the most ominous of any, and the most difficultsign to deal with. We'd like to prove liver involvement or liver disturbances at an early phase hoping to prolong the survival of the patients with early liver involvement in stage-IV.

I agree also with him in his presentation of the difference in the response to chemotherapy in patients who started out with early disease and who have run a

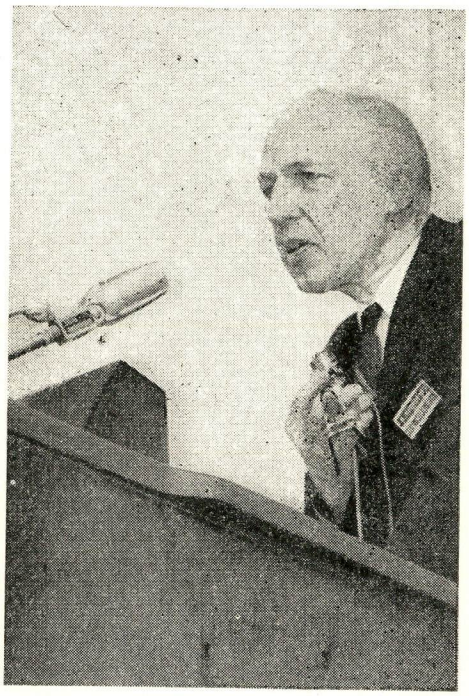
fairly chronic course, as opposed to the patient with very aggressive disease who presents in a fairly late stage, possibly Stage-IV. These are two entirely different groups of patients and respond in a very different manner both to chemotherapy and to additional attempts to control the disease by radiation therapy.

Dr. Karnofsky has reviewed many of the individual clinical features pertaining to the individual patient with HD, which suggest a good prognosis or a poor prognosis. I am in agreement with all the factors which he mentioned. I might add one individual feature which is helpful in anticipating the expected course of the disease, and that is the difference between massive involvement in lymph nodes and minimal involvement in lymph nodes, regardless of the stage. We have two parallel patients in stage I or II, or III or IV. The patient with more massive involvement of the lymph nodes will respond better to treatment than the patient with the small lymph node pattern. This is not what you would expect to find except that the patients with the large lymph nodes have disease we are better able to identify. In the small lymph node pattern one can nearly always guess that there are small lymph nodes elsewhere in occult areas which is impossible to identify. They seem to represent two different types of patients. This is the only minor factor which I have to add to all the influences which have been mentioned by the panel.

This round table was tape recorded and this transcription was not revised by the participants (The Editor).

THE ROLE OF CHEMOTHERAPY IN THE TREATMENT OF HODGKIN'S DISEASE*

DR. DAVID A. KARNOFSKY



I want to take this opportunity to thank the members of the Brazilian Health Service and the National Cancer Institute for inviting me to participate in this Symposium. It's been an instructive and pleasurable experience.

The size and resources of Brazil are overwhelming and the opportunities unlimited, and on each visit here one is stirred by how much more has been done and yet what still remains to be done. The common interest in the achievements and progress of Brazil and the United States unites us as much as do the ties of our profession.

The use of drugs in the chemotherapy of lymphomas began in 1942, 25 years ago, during World War II, when Goodman, Gilman, **et al.** (1) under conditions of military secrecy administered a derivative of nitrogen mustard, tris (B-chloroethyl) (HN3), to patients with leukemias and lymphomas. A year later, in 1943, Dr. Leon Jacobson, of the University of Chicago, studied methyl bis (B-chloroethyl) amine (HN2) under the same secret precautions, since HN2 was a potential war gas, and observed therapeutic responses in Hodgkin's disease. Following the end of World War II, the first published reports appeared on the use of nitrogen mustard in the treatment of Hodgkin's disease (2, 3, 4).

Since 1947 many potential anti-cancer drugs have been tested for therapeutic activity against neoplastic disease in man, and in almost every instance the drugs have been evaluated also in patients with Hodgkin's disease.

Polyfunctional alkylating agents

The different categories of drugs that have been tried include the nitrogen mustard group, which are also referred to as the "polyfunctional alkylating agents". More than 50 functional alkylating agents have been prepared for clinical trial. Following the clinical studies with HN2 and HN3, triethylene melamine (TEM) was widely used, because it was effective by both the oral and intravenous routes (5). Chlorambucil became available in 1954 and has been used extensively by the oral route, and in 1957, cyclophosphamide (Cytoxan, Endoxan) was developed for oral and intravenous administration.

Advantages of the new derivatives are: 1) they are effective and usually well-tole-

---

* Transcrição de gravação, revisto o original pelo autor. This investigation is supported in part by the INC grants CA-08748 and CA-05826.

rated by mouth and, 2) in contrast to nitrogen mustard, they can be given intravenously without causing severe nausea and vomiting. There is little evidence that one alkylating agent has any greater specificity for Hodgkin's disease than another, or that it will produce a more selective therapeutic response at doses causing less severe injury to the bone marrow. Some clinicians believe, however, that cyclophosphamide produces less platelet depression than the other alkylating agents, at equivalent therapeutic doses, and, therefore, recommend its use when bone marrow function is impaired.

Antimetabolites and Antibiotics

Antimetabolites, including methotrexate, 6-mercaptopurine, and 5-flourouracil, have been evaluated in Hodgkin's disease, and none appears to have an important role in the treatment.

Antibiotics, such as Actinomycin D, streptonigrin, and mitomycin-C, have been used in Hodgkin's disease and, while they have produced objective evidence of benefit, they are not as effective as other available drugs.

Adreno-cortical hormones first became available for clinical use in 1949. They have been used extensively in Hodgkin's disease, and prednisone is the most widely used derivative. There is a specific indication for prednisone in acquired hemolytic anemia, but it should not be used as a primary form of treatment or as a supportive measure during the major course of the disease. They are largely employed in the patients with very far advanced disease refractory to other forms of treatment, when brief periods of symptomatic improvement may result (7).

Vinca alkaloids

These became available about 1960 and both vinblastine and vincristine have important indications in the relief of symptoms and control of systemic disease (8).

N-methylhydrazine (Procarbazine, Natulan)

This agent was developed in Switzerland, and it is the most recent addition to the group of drugs active in Hodgkin's disease (9).

The use of drugs in the management of Hodgkin's disease will be discussed under 5 headings:

1. Techniques of evaluation for therapeutic activity.
2. Properties of the presently available drugs,
3. Evidence for therapeutic activity in patients,
4. Indications in specific clinical situations, and
5. Experimental approaches to enhance chemotherapeutic activity.

1. **Techniques of evaluation for therapeutic activity:** In testing drugs for therapeutic activity, the evidence for a favorable effect in Hodgkin's disease is based on suppression of manifestations of the disease, such as a decrease in the size of enlarged lymph nodes, liver and spleen, decrease in fever and itching, increase in well-being, etc. It has not been feasible, with the drugs thus far evaluated, to measure their effect on survival time since favorable responses are usually brief and must be maintained by frequent courses of treatment. If a drug produces a prolonged or permanent disappearance of the signs and symptoms of the disease in a significant per cent of treated patients, prolongation of survival will become apparent, but this has not been the case for the drugs now in use.

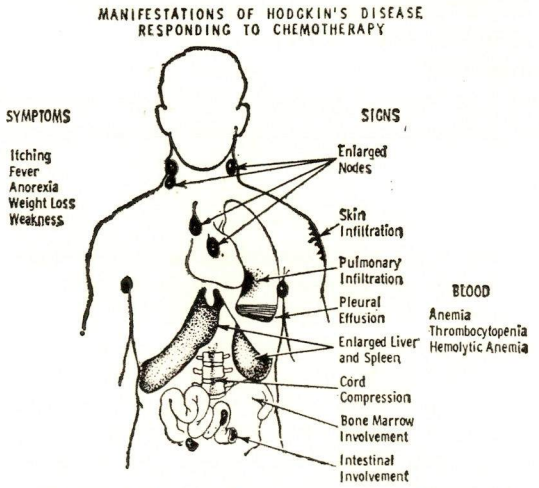


Figure 1 demonstrates some of the major manifestations of Hodgkin's disease which may be modified by chemotherapy, and are

useful in measuring the therapeutic activity of a drug. Each patient, prior to treatment, has the important abnormalities due to the disease listed, such as cutaneous manifestations, pulmonary infiltrates, effusions, hepatosplenomegaly, bone marrow involvement, anemia, thrombocytopenia, fever, weight loss, weakness, etc. After an adequate trial of treatment, the degree and duration of improvement in the listed criteria are determined, e.g., regression of enlarged nodes and decrease in fever. Besides these specific changes, we are interested in measuring the overall benefit to the patient in terms of his performance status (PS) (Table 1). If the patient had a performance status of 60 prior to treatment because of a high fever, weakness and inability to do useful work, restoration to normal activity, PS 90, represents substantial benefit. In contrast, a patient may show objective regression of lymph nodes and relief of fever without significant change in his PS, which remains at 60; the beneficial effect of the treatment in this situation may not be apparent to the patient.

TABLE 1
CRITERIA OF PERFORMANCE STATUS (PS)

	%	
ABLE TO CARRY ON NORMAL ACTIVITY; NO SPECIAL CARE IS NEEDED.	100	Normal; no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort some signs or symptoms of disease.
UNABLE TO WORK; ABLE TO LIVE AT HOME; CARES FOR MOST PERSONAL NEEDS; A VARYING AMOUNT OF ASSISTANCE IS NEEDED.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires ocasional assistance but is able to care for most of his needs.
	50	Requires considerables assistance and frequent medical care.
UNABLE TO CARE FOR SELF; REQUIRES EQUIVALENT OF INSTITUTIONAL OR HOSPITAL CARE; DISEASE MAY BE PROGRESSING RAPIDLY.	40	Disabled; requires special medical care and assistance.
	30	Severely disabled; hospitalization is indicated, although death not imminent.
	20	Very sick; hospitalization necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead.

We have also developed a simple classification of **Category of Response** of the patient to a particular drug, so that we can compare the results obtained with different drugs in terms of suppression of the manifestations of the diseae (Table 2). Patients obtaining a O-A, B, or C category of response may show some drug effect, which may be of scientific interest, but the response is without significant benefit to the patient. Category I responses refer to significant degrees of improvement which are of practical value to the patient. It is necessary to treat a substantial group of patients in order to arrive at a picture of the drug's range and duration of effectiveness, and the results of treatment in each case must be related to the degree of toxicity induced by the drug.

As Dr. Ultmann noted earlier, there is a definite association between the frequency, degree and duration of improvement to

treatment and the inherent rate of progression of the disease. If the disease is rapidly progressive, the response is generally brief, whereas it is more complete and prolonged in patients with a less severe form of Hodgkin's disease. The duration of improvement may, therefore, correlate better with the activity of the disease than with the efficacy or lack of efficacy of a particular drug. Nevertheless, the effective agents noted do appear to have some degree of specificity, in that a patient refractory to one class of drug, such as an alkylating agent, may respond to a vinca alkaloid or procarbazine.

TABLE 2

CATEGORIES OF RESPONSE

CATEGORY 0 NO CLINICALLY USEFUL EFFECT ON THE COURSE OF THE DISEASE

0 — 0	Disease progresses — no objetive or subjective benefit.
0 — A*	Subjective benefit without favorable objective changes.
0 — B*	Favorable objective changes without subjective benefit.
0 — C	Subjective benefit and favorable objective changes in measurable criteria, but of less than one montn's duration; then the disease progresses.

CATEGORY I CLINICAL BENEFIT WITH FAVORABLE OBJECTIVE CHANGES IN ALL MEASURABLE CRITERIA OF THE DISEASE

I — A*	Distinct subjective benefit with favorable objective changes in all measurable criteria for one month or more.
I — B*	Objective regression of all palpable or measurable neoplastic disease for one month or more in a relatively asymptomatic patient, who is able to carry on his usual activities without undue difficulty. The observed tumor regression should be unequivocal and it is suggested that all lesions be reduced at least 50% in bulk. This category applies as long as the regression persists, and ends if any lesion old or new recurs.
I — C	Complete relief of symptoms, if any, and regression of all manifestations due to the active disease for one year or more. The relation to the frequency of therapy is not relevant, if the disease does not recur between courses of therapy.

* Categories apply as long as improvement from baselines persists. Superscript: time in months of duration of response. Example : $0 — A^4$ or $I — B^3$.

CATEGORY II INTERRUPTION OR SLOWING IN THE PROGRESSION OF THE DISEASE WITHOUT DEFINITE EVIDENCE OF SUBJECTIVE OR OBJECTIVE IMPROVEMENT. No criteria are presently available to classify this type of response. Statistcial evidence of prolongation of survival time in specific patterns of cancer may some day be applicable.

ADEQUATE THERAPY

The adequacy of the course of treatment should be defined in the patients who complete the course of treatment. In most cases therapy is given to the of toxicity in order to give the maximum opportunity for an anticancer effect. If the patient can be observed following treatment for at least two weeks for signs of benefit, this ordinarily represents an adequate trial.

If tumor regression and a satisfactory clinical response occur before signs of toxicity appear, this is also considered an adequate trial.

LEVELS OF TOXICITY

1 + —	Slight
2 + —	Moderate
3 + —	Life threatening — patient recovers
4 + —	Directly lethal or a proximate contributory cause of death

2. **Properties of the presently available drugs:** The drugs used in the treatment of Hodgkin's disease are well know, and they will be reviewed briefly:

Nitrogen mustard (Mustargen, HN2). This is the earliest and one of the most widely used polyfunctional alkylating agents. It is given intravenously, and the usual dose is 0.4 mg/Kg. of body weight. We generally give this as a single dose if the patient has normal bone marrow function and is in good general condition. If there is any question about the patient's status we may fractionate the dose, 0.2 mg/Kg. as asingle dose repeated in a few days if the blood picture is satisfactory. At therapeutic doses, the alkylating agents may produce a decrease in the leucocyte and platelet counts and hemoglobin level. If the patient receives an excessive dose, this will result in bone marrow depletion, with increased susceptibility to infection and bleeding manifestations. HN2 as well as the other alkylating agents must be used cautiously, since maximal change in the peripheral blood picture may not occur for 2 to 3 weeks after the last dose. The use of these agents, therefore, requires frequent examinations of the peripheral blood picture. HN2 is used principally in acute situation, when a rapid response is required, such as spinal cord compression, superior vena cava syndrome or respiratory distress due to Hodgkin's disease. In ambulatory patients, where maintenance therapy is feasible, alkylating agents without the acute gastro-intestinal effects of HN2 are preferred.

An alternative to HN2 is intravenous **thio-TEPA.** In comparative studies it appears to have a therapeutic action similar to HN2, and it has the advantage of causing less nausea and vomiting. The total dose is generally about twice that of HN2 by weight; we generally give 0.8 mg/Kg. as compared to 0.4 mg/Kg. of HN2. If the patient will not take an oral alkylating agent as directed, thio-TEPA intravenously, 0.2 to 0.4 mg/Kg. once a week or every other week, may be a satisfactory form of maintenance therapy.

Of the oral alkylating agents, we prefer **chlorambucil** in most situations. The usual dose is 0.1-0.2 mg/Kg. (6-12 mg) each day, and a favorable response may occur in 2 to 3 weeks or sooner. The dose must be decreased in patients with poor bone marrow function, and in all cases the blood count must be followed at weekly intervals. If the patient responds, a maintenance dose of 2-4 mg/day may be effective. This should be interrupted periodically to allow the bone marrow to recover, if meanwhile the disease is being controlled satisfactorily.

Cyclophosphamide may be given orally or intravenously. The intravenous dose, equivalent to 0.4 mg/Kg. of HN2, is 40 mg/Kg. or about 100 times as much by weight. This dose can be decreased or fractionated if there is concern about the patient's bone marrow function. Cyclophosphamide causes less nausea and vomiting than nitrogen mustard. The daily oral dose is in the range of 1-3 mg/Kg. (50-200 mg), and this can be given daily for long periods. The chief disadvantages of cyclophosphamide are the occurrence of cystitis, which may be hemorrhagic, and temporary alopecia. There is a clinical impression that cyclophosphamide is more useful than the other alkylating agents in reticulum cell sarcoma.

A second class of drugs in Hodgkin's disease is the vinca alkaloids, **vinblastine** (Velban) and **vincristine** (Oncovin). **Vinblastine** differs from vincristine only in the presence of a methyl in place of a formate group, but this produces a considerable difference in their pharmacological properties. Vinblastine is generally the preferred derivative in Hodgkin's disease. It is usually given intravenously once a week, in the dose range of 0.1 to 0.3 mg/Kg. We begin at the lower dose ,and if a satisfactory response occurs, this same dose is continued; otherwise, it may be raised each week to 0.15-0.20 mg/Kg. if the blood picture allows. A maintenance schedule can be established in the responsive patient, and 0.1 mg/Kg. given at weekly or every other week injections. The most important toxic effect of vinblastine is bone marrow depression, which may be transient, and the blood count should be obtained before each injection. Occasionally some patients develop signs of neurotoxicity, including a peripheral neuritis, ileus, constipation, as well as alopecia and stomatitis. **Vincristine** is used in patients with impaired bone

marrow function, since the neurotoxicity is generally the limiting factor in dosage. The usual dose is 0.01-0.025 mg/Kg. (0.6-2.0 mg) intravenously each week. The patient must be followed carefully for a loss of deep tendon reflexes and neurotoxicity. If a response is obtained at 0.025 mg/Kg., a maintenance level may be established in the range of 0.01-0.015 mg/Kg. each week.

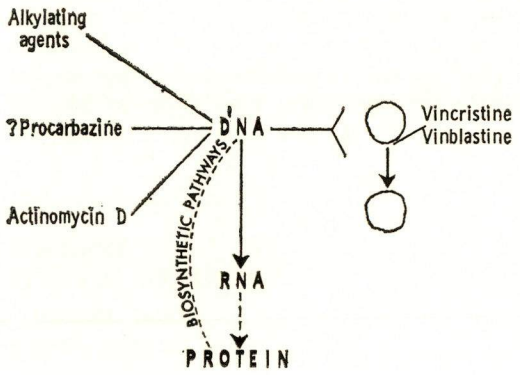
A third class of drugs is the **adreno-cortical hormones,** of which **prednisone** is the principal representative. When prednisone is used in far-advanced Hodgkin's disease, no longer responsive to alkylating agents, vinblastine or x-ray therapy, we generally begin with a large dose, in the range of 60-100 mg/day, and if significant improvement occurs, this dose can be reduce to maintenance levels, although generally large doses are necessary. In hemolytic anemias, a smaller dose may be adequate.

The newest drug for Hodgkin's disease is **procarbazine** (Natulan). This drug is still an experimental agent in the United States, and has not been approved by the Food and Drug Administration for commercial sale. Procarbazine is given orally, at a daily dose ranging from 50 to 300 mg/day. One generally begins with the smaller dose, and as the patient becomes acclimated, the dose is increased. The nausea and vomiting, which often occur at the onset of treatment, tend to disappear as treatment continues. After 2-3 weeks at a dose of 200-300 mg/day, when the blood picture begins to be adversely affected, the dose is temporarily interrupted or reduced to a maintenance level in the range of 50 mg/day. Procarbazine is active in Hodgkin's disease, but its indication in relation to the other drugs available, has not been defined.

Actinomycin D (Cosmegen) has been effective in Hodgkin's disease, but it is not as useful or as well tolerated as the other agents described, and we no longer recommend it.

It is interesting to consider the site of action of drugs which influence some of the manifestations of Hodgking's disease. Figure 2 shows the classical sequence in cellular growth and function; DNA producing RNA, including messenger RNA, which in turn directs the synthezis of specific proteins or

CELLULAR EFFECTS OF DRUGS USED IN HODGKIN'S DISEASE



enzymes. Replication of DNA precedes cell division. Of the many drugs studied in Hodgkin's disease, the effective ones appear to act on DNA, either altering its structure or interfering with its funcion. The alkylating agents and procarbazine have been shown to damage DNA, Actinomycin D interferes with the formation of DNA-dependent RNA, and the vinca alkaloids inhibit mitosis. The drugs which interfere with biosinthetic pathways in proliferating cells have been weakly active or ineffective in Hodgkin"s disease. At present there are no data on the specific cells in Hodgkin's disease susceptible to the anti-cancer drugs which results in regression of enlarged nodes, and alleviation of systemic symptoms. Are the neoplastic cells the ones that are being damaged directly or is a normal cellular reaction to the neoplastic cells being suppressed? This is a problem ready for intensive investigation.

3. **Evidence for therapeutic activity in patients:** In quantitating the therapeutic activity of an anti-cancer drug in Hodgkin's disease, it has been noted earlier that the individual patient's response varies with the clinical activity of the disease; if the patient is in good general condition, with rather indolent disease, the response to any effective agent may be complete and prolonged. If the patient has a more acute process, and if he is refractory to radiotherapy and to other chemotherapeutic agents, the response to a new form of treatment is usually poor. Reported response rates to specific agents are largely meaningless, unless the clinical status of the patients

treated is described in detail and the type of response clearly stated. With the alkylating agents, for example, one can expect a Category I response rate of 90% if the drug is used as the first treatment; late in the disease response rate may drop to 60% or less. A generalization, with many exceptions, is that the response rates to the effective agents againts Hodgkin's disease are approximately the same in patiens in similar circumstances, although patients refractory to one agent may sometimes respond temporarily to another type of drug. In Tables 3 and 4 are listed recent data on

TABLE 3

HOGDKIN'S DISEASE

CLINICAL EFFECTS OF IV VINBLASTINE

Total number of patients = 79
Number adequate = 79

Category of response	Number	Numbers of patients/duration of responses Months												
I — C	7	13	14	15	16	17	18	19	20	21	22	23	24	36
		2	1+			1						1	1+	1
		Months												
I — A	35	1	2	3	4	5	6	7	8	9	10	11	12	
I — B	6	10	7	4	2	2	2	1	1	2	2	2		
O — A, B														
C, II	23		2			2	1	1	1					
O — O	8													

This table is reproduced with the king permission of the authors MacDonald and Lacher (11).

TABLE 4

HOGDKIN'S DISEASE

Total number of patients = 79
Number adequate = 56

Category of response	Number	Numbers of patients/duration of responses Months													
I — C =	1														
I — A =	33	1	2	3	4	5	6	7	8	9	10	11	12	13	14
I — B =	1														
O — C =	6														1+
O — B =	1							1							
O — A =	4	10	11	3	4	1	2				2				
O — O —	10														
Too early to evaluate =	2														

This table is reproduced with the kind permission of the authors Brunerr and Young (9).

categories of responses with vinblastine (11) and procarbazine (9). Of 79 patients receiving an adequate course of intravenous vinblastine, 48 had a Category I response, ranging from 1 month to 36 months. Of this group, 7 had a I-C response, in that all evidence of disease disappeared for one year or longer. Seventy-one of the 79 (90%) patients showed evidence of therapeutic effects from vincristine, but in 23 the response was brief and inconclusive.

Of 53 patients receiving an adequate course of procarbazine (Table 4), 35 (62%) obtained a Category I response, and 46 of the 56 patients (82%) showed some evidence of therapeutic activity, although in 11 cases it was of no significant benefit to the patient. The duration of improvement with procarbazine was considerably shorter than with vinblastine, 1-2 months as compared to 4 months, but this may be due, in part, to case selection. We are attempting to develop better methods of presenting clinical result in order to clarify comparative therapeutic activity of chemotherapeutic agents.

4. **Their indications in specific clinical situations:** How does the physician know which drug to use in a specific clinical situation; should he give vinblastine, vincristine, chlorambucil or nitrogen mustard? There are no firm rules, because much of the basis for a decision depends on the physicion's training, experience with various agents, availability of x-ray therapy, and his analysis of the clinical problem. All that one can emphatically recommend is that the physician analyze the situation carefully, review the patient's previous treatments and the responses that occurred, and define in his own mind what he hopes to accomplish by a particular method of treatment. He should then act deliberately, and give each drug an adequate trial before turning to another form of treatment. I can briefly comment on some of our own preferences in the use of these drugs.

For acute situations, such as impending cord compression or acute respiratory distress due to superior vena cava compression, we prefere nitrogen mustard, although thio-TEPA may be an equally effective alternative. We have more confidence in the dose of nitrogen mustard that is both safe and effective. If the patient is ambulatory, and does not require a rapid course of treatment, chlorambucil is the oral alkylating agent of choice. We prefer using an alkylating agent as the first drug, and if the patient becomes resistant to it, vinblastine is the second agent. If serious bone marrow depression exists, vincristine would be used instead of vinblastine. Procarbazine is the third agent, and prednisone may be used in the advanced stages of the disease. We use one drug at a time because it is easier to follow the patient in terms of giving an adequate dose, and the therapeutic activity of this drug can be interpreted.

The major indication for chemotherapy is the patient with generalized disease and systemic symptoms, such as fever, itching, weight loss and anemia which has not been controlled by localized x-ray therapy. In the situations the use of drugs may suppress symptoms and keep the patient in good condition for long periods. We maintain a close liason with our radiotherapists, and while chemotherapy is used to try to alleviate symptoms, in many cases persistent local disease is treated with radiotherapy. If indicated, or, to put it another way, we are not alarmed by a depressed leucocyte count due to chemotherapy if local radiotherapy is required. As the disease advances, one must be prepared to accept greater risks from treatment in the hope of obtaining clinical improvement.

5. **Experimental approaches to enhance chemotherapeutic activity:** Finally, I will comment briefly on some experimental problems in the treatment of Hodgkin's disease. A distinction should be made between the use of anti-cancer drugs in a convencional and acceptable manner, and their use in a controlled study under experimental conditions. If a patient is being managed in a convencional manner, one may modify the treatment, or add other drugs in the interests of total patient care. In a controlled study, the patient is being managed under a carefully developed protocol, and treatment is continued until the study is completed. In beginning a controlled study, there must be some preliminary evidence to

suggest that the design of the study will lead to a meaningful conclusion. In Table 5 are listed several current therapeutic programs, of many in progress.

TABLE 5
HODGKING'S DISEASE
EXPERIMENTAL CHEMOTHERAPY

1. ADJUVANT	—	Alkylating agent with local x-ray Rx
2. INTENSIVE CHEMOTERAPY	—	Single drug or combination
3. COMBINATION	—	Vinblastine + Chlorambucil
4. NEW DRUGS	—	Daunomycin
		Imidazole carboxamide dimethyltriazeno
		Cycloheximide (for fever)

a. **Adjuvant chemotherapy**. En 1949 we began a program of using a course of nitrogen mustard in combination with intensive radiotherapy for localized Hodgkin's disease (12). This involved the injection of 0.4 mg/Kg. HN2 followed by a tissue dose of 3000 rads delivered to the involved area and adjacent lymph nodes. This schedule was well-tolerated, and we had the impression that nitrogen mustard contributed to the prolonged control of the disease in the irradiated area; disease reappeared outside the irradiated area in some cases, indicating that nitrogen mustard by itself not act prophylactically to eliminate areas of occult disease. This preliminary study has now been organized under a formal protocol.

b. **Intensive chemotherapy**. The National Institutes of Health and cooperating groups in the United States have initiated a far more intensive chemotherapy program, designed to try to obliterate cell foci of Hodgkin's disease. A combination of nitrogen mustard, vincristine, procarbazine and prednisone has been given in repeated courses at the maximum tolerated dose. In one schedule these drugs are administered during a two week period, and the treatment is interrupted until bone marrow recovery occurs, and the treatment cycle is repeated three times. This is an experimental study, a physician should not undertake it in an isolated patient until there is sufficient evidence available to demonstrate the efficacy of this approach. The combination is being evaluted in localized as well as in advanced Hodgkin's disease.

Another approach has been the use of continuous chemotherapy in patients in whom the disease is apparently under satisfactory control following localized radiotherapy. Patients have been placed on vinblastine, chlorambucil or on combinations of drugs for long periods in the hope of preventing a relapse. This, in my opinion, is not a reasonable use of the presently available anti-cancer drugs.

c. **Combination therapy**. Some of the anti-cancer drugs are being used in combinations, in place of a single drug. Lacher and Durant (13) have presented evidence that patients not responding satisfactorily to vinblastine or chlorambucil separately, may show grater improvement on the combination.

d. **New agents**. Several new agents are under investigation, including daunomycin (14), an Italian antibiotic, imidazole carboxamide dimethyltriazeno (ITC) and actidione (15). The latter has specifically prevented the fever of Hodgkin's disease, although it is effective only during the period of drug administration.

The approaches represent investigational areas of chemotherapy. The list will change as new approaches are developed, and the current studies are completed.

SUMMARY AND CONCLUSIONS

Chemotherapeutic agents have been used in the treatment of Hodgkin's disease for more than 25 years, and their value is clearly established. The important groups are :

1. the polyfunctional alkylating agents,
2. the vinca alkaloids,
3. procarbazine, and
4. the adrenal steroids.

These agents are principally indicated in widespread symptomatic Hodgkin's disease.

We prefer to use one agent at a time, and evaluate its effects before considering the use of another. When chemotherapy is advisable, our present preference is to start with an alkylating agent and, if the patient becomes refractory to it, a vinca alkaloid, and then procarbazine; prednisone may be useful in the late stages of the disease. Some clinicians, however, prefer vinblastine as the initial form of treatment. Some of the experimental approaches in the chemotherapy of Hodgkin's disease have been noted, including the combination of x-ray therapy and chemotherapy, combinations of active anti-cancer drugs, and trials of new agents.

REFERENCES

1 — GOODMAN, L , WINTROBE, M. M., DAMESHEK, W., GOODMAN, M. J., GILMAN, A., and MCLENNAN, M. T.: Nitrogen mustard therapy; use of methyl-bis(*B*-chloroethyh)amine hydrochloride and tris(*B*-chloroethyl)amine hydrochloride for Hodgkin's disease, lymphosarcoma, leukemia and certain allied and miscellaneous disorders. JAMA *132*: 126, 1946.

2 — JACOBSON, L. O., SPURR, C.L., GUZMAN BARRON, E. S., SMITH, T., LUSHBAUGH, C., and DICK, G. F.: Nitrogen mustard therapy; studies on the effect of methyl-bis(*B*is-chloroethyl)-amine hydrochloride on neoplastic diseases and allied lisorders of the hemopoietic system. JAMA *132*: 263, 1946.

3 — WINTROBE, M. M., MCLENNAN, M. T., and HUGULEY, C. M., Jr.: Clinical experiences with nitrogen mustard therapy. In: Approaches to Tumor Chemotherapy, p. 347. Washington, D. C., Am. Assoc. Advancement Science, 1947.

4 — KARNOFSKY, D. A., BURCHENAL, J. H., ORMSBEE, R. A., CORNMAN, I., and RHOADS, C. P.: Experimental observations on the use of the nitrogen mustards in the treatment of neoplastic diseases. In: Approaches to Tumor Chemotherapy, p. 293. Washington, D. C., Am. Assoc. Advancement Science, 1947.

5 — KARNOFSKY, D. A., BURCHENAL, J. H., ARMISTEAD, G. C., Jr., SOUTHAM, C. M., BERNSTEIN, J. L., CRAVER, L. F., and RHOADS, C. P.: Triethylene melamine in the treatment of neoplastic disease; a compound with introgen-mustard-like activity suitable for oral and intravenous use. A.M.A. Arch. Int. Med. *87*: 477, 1951.

6 — Conference on Hodgkin's disease, New York, November 25-26, 1957. In: Ann. N. Y. Acad. Science *73*: 1-380, 1958.

7 — Hall, T.C.; Choi, O.S.; Abadi, A.; and Krant, M. J. — High dose corticoid therapy in Hodgkin's Disease and other Lymphomas, Annals of Internal Med. *66*: 1144-1153, 1967.

8 — KARNOFSKY, D. A.: Chemoterapy of Hodgkin's disease. Cancer *19*: 371, 1966.

9 — BRUNNER, K. W., and YOUNG, C. W.: A methylhydrazine derivative in Hodgkin's disease and other malignant tumors; therapeutic and toxic effect studied in 51 patients. Ann. Int. Med. *63*: 69, 1965.

10 — KARNOFSKY, D. A. : Meaningful clinical classificiation of therapeutic responses to anticancer drugs. Clin. Pharm. Therapeutics *2*: 709, 1961.

11 — MACDONALD, C. A., and LACHER, M. J.: Oral vinblastine sulfate in Hodgkin's disease. Clin. Pharm. Therapeutics *7*: 534, 1966.

12 — KARNOFSKY, D. A., MILLER, D. G., and PHILLIPS, R. F.: Role of chemotherapy in the management of early Hodgkin's disease. Am. J. Roentgenology, Rodium Therap. and Nuclear Med. *XC*: 968, 1963.

13 — LACHER, M. J., and DURANT, J. R.: Combined vinblastine and chlorambucil therapy of Hodgkin's disease. Ann. Int. Med. *62*: 468, 1965.

14 — TAN, C., TASAKA, H., YU, K.-P., MURPHY, M. L., and KARNOFSKY, D. A.: Daunomycin, an antitumor antibiotic, in the treatment of neoplastic disease; clinical evaluation with special reference to childhood leukemia. Cancer *20*: 333, 1967.

15 — YOUNG, C. W., and KARNOFSKY, D. A.: The necessity of protein synthesis for fever in Hodgkin's disease. Proc. Am. Assoc. Cancer Res. *8*: 75, 1967 (Abstract).

Dr. John E. Ultmann

Surgery as the definitive therapy of Stage I Hodgkin's disease has no advantage over agressive radiotherapy directed to the involved lymph nodes and to adjacent areas.

The most frequent indication for surgery in the management of Hodgkin's disease is biopsy for diagnosis. Usually, a superficial lymph node is biopsied. The surgeon should choose a large node, preferably one **not** located in the inguinal area. A portion of the lymph node may be sent to the laboratory to search for tuberculosis, toxoplasmosis or other organisms. When lymph nodes are not readily accessible for biopsy, consideration is given to thoracotomy or laparotomy. Occasionally, the diagnosis is made following laminectomy or splenectomy.

In the course of Hodgkin's disease, certain complications arise which may lead to surgical intervention. Laminectomy should be done in those patients with chord compression whose symptoms are of recent origin and progressing rapidly, and whose lesion can be localized. Laminectomy is indicated particularly in the presence of vertebral bone destruction. Relief of obstruction or hemorrhage secondary to gastro-intestinal Hodgkin's disease may require surgical intervention. More rarely, obstructive uropathy may require temporary nephrostomy. Following surgical intervention in these complications, radiotherapy is usually indicated. Splenectomy may be performed, at times, in patients with hypersplenism. The very high operative mortality, together with the short survival periods of those patients surviving operation, lead Grace and Mittelman to conclude that splenectomy in this group of patients has a very limited indication. Selection of patients with clinical problems **largely** due to hypersplenism is essential. Red cell survival and sequestration studies are very useful in selecting candidates. The improvement following splenectomy may be striking, as evidenced by red cell survival studies changing from T/2 11.2 days pre-splenectomy to T/2 27 days post-splenectomy. A rise of hemoglobin values of 4 to 6 gram % occurred in 6 of 13 cases. Granulocytes and platelets increased substantially in 6 and 8 cases, respectively, of 13 patients studied.

For control of intractable pain, neurosurgical intervention — including alcohol blocks, chordotomy and other procedures — may at times be indicated.

Grace and Mittelman have summarized recently the role of surgery in the over-all management of Hodgkin's disease, noting that it is limited to excision for diagnostic purposes and to the management of unrelated problems which might require surgical intervention.

we do treat the patients with other things and we're really not truly evaluating Indocin by itself, but in some individuals who were getting aspirin and who were actually getting steroids and had dailly fever of 103 or 104 and who could not be given an alikilating agent or Velban because of severe bone marrow toxicity, might be tied over at a lower temperature level such as 101°, that would be 38° C, rather than 40° C. We have not encountered any toxicity so far but there are a number of things to look for which I don't, at this moment want to go into. It is very well tolerated and for brief periods of 2 to 3 weeks may be just the useful thing to do till you can turn to something else.

Dr. Henry S. Kaplan:

Thank you. I think this is the point that has impressed me in a small number of cases, perhaps 4 or 5 cases. We have seen patients in whom we know that there was no response to aspirin or to steroids, in which Indocin has brought about a prompt suppression of fever. They have been quite confortable and the virtue of this is not that the disease process is specifically affected but that in some of these cases at least we have seen this interval result in a return of what appeared to be an exhausted bone marrow. So that after a total of 4 to 5 weeks on Indocin, in which patients were maintained in a state of considerable confort, it was again possible to resume specific therapy which would not otherwise have been possible. I think in that sense it may have something more to offer than much of the other non-specific therapies.

I would like to raise a question which I think again both of our speakers migh comment on. For many years, as you know, it has been said that chemotherapeutic agents have not prolonged life in the malignant lymphomas, including HD. I think that most of the early evidence strongly indicated that this was the case. However, in recent years we have witnessed as you've heard this morning, the introduction of a number of new agents, and some these agents seem to be effective after other agents have exausted their usefulness. One can again get a significant duration of remission as you've heard, a 10 month average duration with Velban, a 5 month average duration with Methylhydrazine. These drugs are used one after another and one can't help but feel ,as I have observed, our chemotherapy program, under Dr. Rosenberg, that today the older view that life is not prolonged, may no longer be true. As more and more good and effective agents are introduced, even though they still do not offer cure, I think that they are beggining to offer significant prolongat'on of life. I know that this is an unorthodox point of view and I want to introduce it for both Dr. Karnofsky and Dr. Ultmann to discuss.

Dr. John E. Ultmann:

I believe that in order to discuss this, two points ought to be made in the introduction. The first point is: that we want to be absolutely sure that we do not convey the idea that a single patient has ever been cured by chemotherapy. All we can really hope to look for is prolongation and palliation, compatible life that has been prolonged, but no cure, no cure. Again we must say this no matter what is going to come up next in our discussion.

The second point is that since the majority of patients who receive chemotherapy have had some experience with radiotherapy, and since the majority of patients whom received one chemotherapeutic agent eventually receive at least another, if not others, it is going to be virtually impossible to say for any group of patients that this agent or that agent has prolonged the life of a group of patients. All one can really do is look at this in a sweeping, panoramic point of view.

If you took our own series where there were 115 patients with Stage-III from 1951 to 1964, none of them treated with Velban or Methylhydrazine, there was a 5 year survival of 23%, which I say with pride, it's rather good when you consider that for Stage-III disease the 5 year survival in the literature has ranged, (originally Stages III and IV I should say), has ranged originally from 10% to about 20%. The first point I'd like to make is, I believe that the survival rate is a little better in our series because we've used a little less chemotherapy with the alkylating agents. We've been cautious because there's ample evidence that an occasional patient is harmed by over-enthusiastic chemotherapy. If then, to

this 23% 5 year survival you unitotally do what Dr. Kaplan suggests, that is, you add what appears to be an extension of about 8 or 10 months, actually from 4 months to 18 months of life with Velban, which about 60% of the patients could achieve in our statistical analysis, and if you then add the possibility of a 5 month survival, which ranges from 2 months to 11 months, with Methylhydrazine, again, at least as shown in our series and in some of Mathé's patients, in patients who have gone through the cycle of 2 other drugs, one at least surmizes that one could, for a typical patient, add these averages. If you do this one would think that certainly life can be extended by at least a year speaking conservatively, and possibily 1 year and ½ for the average patient.

Dr. Karnofsky:

I agree with what Dr. Ultmann has said and I just want to emphasize that life is being prolonged in patients who still have active HD, in other words, these are patients that are not being cured but have reccurrent progressive disease. The question is what is responsible for it, as Dr. Ultmann pointed out; first we have to decide whether one agent is more likely to have been responsible for prolongation of life than another. I don't think that we can attribute prolongation of life to any particular agent. We also have to consider what's happened tc the management of patients with advanced HD. I think this is one of the major progesses that have been made. In our own clinics where we know that patients who previously looked as if they might be on the verge of expiring from the disease, improve on treatment and go on and live another 2, 3 or 4 years. There are many factors that are involved. One is that we are using palliative radiotherapy more aggressively in these patients. We are habilitated, so to speak, in chemotherapy. We have availability of blood transfusions. We have many active supportive measures that have been introduced. In terms of antibiotic control for intercurrent infection which are often life threatning. The treatment of chord-compression which might in the past have been responsible for paralysis and early death, has been controlled in 75% of patients and they go on to another period.

There is a remarkable improvement in the overall attitude and management of the disease, and in which chemotherapy is playing a very important part.

Dr. Henry S. Kaplan:

Thank you very much gentlemen. I think we all appreciate very much the remarks of both Dr. Karnofsky and Dr. Ultmann. I'd like now to close this part of our program and to go on to the presentation by Dr. Robert Lukes on the pathological aspects of Burkitt's Tumor.

ROLE OF SURGERY IN THE TREATMENT OF HODGKIN'S DISEASE

DR. HENRY S. KAPLAN
DR. JOHN E. ULTMANN

Dr. Henry Kaplan

Radical lymph node dissection was at one time rather widely advocated for Hodgkin's disease involving a single chain of lymph nodes. However, in most series in which good results of such surgical treatment haven been reported, postoperative X-ray therapy has also been given, and it seems unwarranted to attribute the good results to the surgical procedure **per se.** The lymph node dissections are cosmetically disfiguring, and in the axilla or inguinal regions may be followed by severe edema and even functional impairment of the extremity. Now that modern megavoltage radiotherapy apparatus has become widely available, the argument for radical surgical dissection of locally involved nodes no longer seems tenable. With doses in the range of 4,000 rads delivered in approximately four weeks, megavoltage radiotherapy can eradicate Hodgkin's disease in entire chains of lymph nodes with a recurrence rate of only 2 to 5 per cent, and with far superior cosmetic results. I can therefore see no justification for the continued use of radical lymph node dissection in Hodgkin's disease.

However, the surgeon still has a useful role to play in the management of this condition. We have observed a number of patients with a palpably or radiographically enlarged spleen, an equivocal lymphangiogram with some paraaortic nodes highly suggestive but not entirely diagnostic of lymphomatous involvement, and questionable liver function tests. In such instances, we have found it extremely useful to proceed with splenectomy, biopsy of the questionable paraaortic nodes, and open liver biopsy. Moreover, splenectomy has been useful in a number of patients with hemolytic anemia and thrombocytopenia due to hypersplenism. After splenectomy, such patients have again exhibited normal white blood cell and platelet counts, and those who had been on chemotherapy have been able to resume treatment safely, with significant prolongation and useful life span in many instances.

* Resumo das apresentações.

Dr. John E. Ultmann

Surgery as the definitive therapy of Stage I Hodgkin's disease has no advantage over agressive radiotherapy directed to the involved lymph nodes and to adjacent areas.

The most frequent indication for surgery in the management of Hodgkin's disease is biopsy for diagnosis. Usually, a superficial lymph node is biopsied. The surgeon should choose a large node, preferably one **not** located in the inguinal area. A portion of the lymph node may be sent to the laboratory to search for tuberculosis, toxoplasmosis or other organisms. When lymph nodes are not readily accessible for biopsy, consideration is given to thoracotomy or laparotomy. Occasionally, the diagnosis is made following laminectomy or splenectomy.

In the course of Hodgkin's disease, certain complications arise which may lead to surgical intervention. Laminectomy should be done in those patients with chord compression whose symptoms are of recent origin and progressing rapidly, and whose lesion can be localized. Laminectomy is indicated particularly in the presence of vertebral bone destruction. Relief of obstruction or hemorrhage secondary to gastro-intestinal Hodgkin's disease may require surgical intervention. More rarely, obstructive uropathy may require temporary nephrostomy. Following surgical intervention in these complications, radiotherapy is usually indicated. Splenectomy may be performed, at times, in patients with hypersplenism. The very high operative mortality, together with the short survival periods of those patients surviving operation, lead Grace and Mittelman to conclude that splenectomy in this group of patients has a very limited indication. Selection of patients with clinical problems **largely** due to hypersplenism is essential. Red cell survival and sequestration studies are very useful in selecting candidates. The improvement following splenectomy may be striking, as evidenced by red cell survival studies changing from T/2 11.2 days pre-splenectomy to T/2 27 days post-splenectomy. A rise of hemoglobin values of 4 to 6 gram % occurred in 6 of 13 cases. Granulocytes and platelets increased substantially in 6 and 8 cases, respectively, of 13 patients studied.

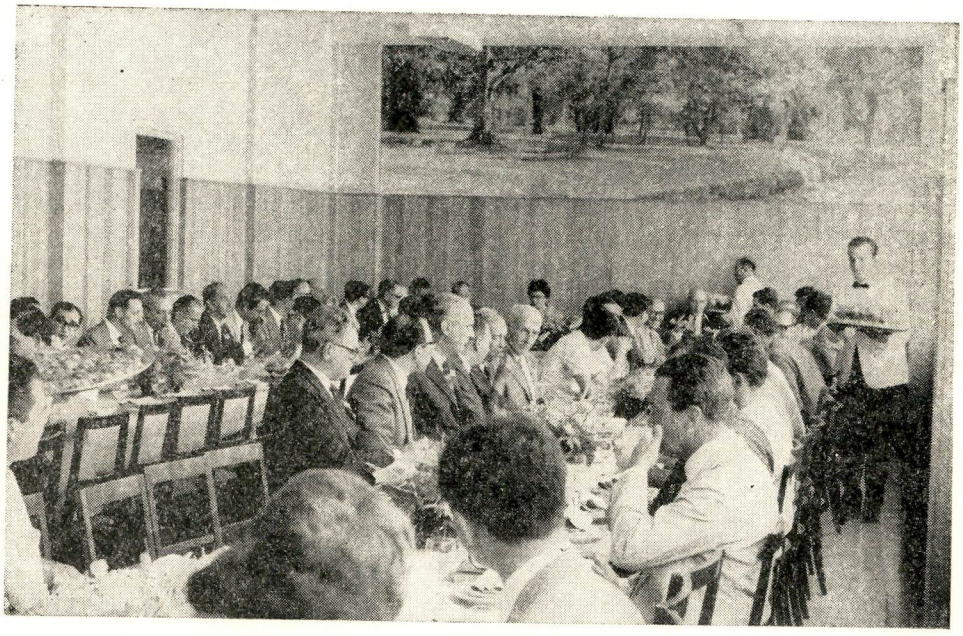
For control of intractable pain, neurosurgical intervention — including alcohol blocks, chordotomy and other procedures — may at times be indicated.

Grace and Mittelman have summarized recently the role of surgery in the over-all management of Hodgkin's disease, noting that it is limited to excision for diagnostic purposes and to the management of unrelated problems which might require surgical intervention.

THE POSSIBILITIES OF CURE OF THE HODGKIN'S DISEASE PATIENT

ROUDN.TABLE LUNCHEON

Chairman: **Dr. Joseph Burchenal**
Members: **Dr. Henry Kap˙an**
Dr. John Ultmann
Dr. David A. Karnofsky
Dr. M. Vera Peters



Dr. Burchenal :

When many of us went to medical school, I think the general feeling was that HD was a generalized uniformly fatal disease of the lymphoid tissue and that there wasn't really very much one could do about it. You could give treatment, little palliative radiation therapy which was thought to make the patient feel better but there was considerable question whether it prolonged the survival time much. Since that time tremendous steps have been taken. You've heard this week a great deal about the possibilities of cure. This round table discussion will be on the possibilities of cure of the HD patient. We start off with Dr. Kaplan.

Dr. Kaplan :

I think that there are really two questions that we could discuss, may be more but the first is: "What kind of evidence do we have or could we look for that would establish that HD patients really are curable?" and secondly, using whatever evidence we have, "What estimates can one make about the prognosis for cure, not just for survival but for cure, in the various stages of HD as our treatment techniques stand at the present time?"

I think many of you know the criteria that were stated by Easson and Russell a few years ago in their paper in the British Medical Journal. The criteria that Russell described essentially has to do with the flattening of the survival curve, so that it becomes paralel to the survival curve for a correspondingly distributed age and sex distribution in the general population. Obviously the nature of the normal curve will depend on the age and sex distribution of the type of tumor that one is discussing. The survival of normal people who are in the age bracket of cancer of the prostate will be very different from that of the expected survival of patients with an age distribution similar to that of HD, where there are many younger patients. One, therefore, would expect that in meeting the criteria of Easson and Russell the survival curve of a treated group of cases should, after some period of time, ultimately flatten out so that it becomes virtually completely flat with deaths thereafter being attributable only to those general causes of death

* Transcrição de gravação **não revista** pelos participantes.

that will affect any other people in the population. This is a good working definition of cure. It has one drawback that is difficult from the standpoint of working toward improving techniques of treatment, and that is it is too slow. One has to wait too many years to get the answer. It is therefore of great importance that we look for other indications of probable cure that we can observe and learn in the time interval after treatment.

I think one other index of cure might be mentioned, in passing, and then I want to discuss briefly the index of cure that we have been interested in.

I think everyone here has had occasionally the experience of observing a patient with HD who has died of some other cause, either due to acute coma or to some acute infectious process that was clinically unrelated to the original HD, and these patients have come to autopsy, careful autopsy has been done, with the previous history of HD known to the pathologist and no evidence of HD has been detectable at autopsy in such patients. There are many such instances on record now but unfortunately in any one Institution they are extremely few, and it is impossible to use such data really to prove very much beyond the unitotal value that the data have. Finally on this point, the criteria that I have been interested in has to do with the time interval from the first course of treatment to the first new evidence of disease. It is logical to assume that no patient died of HD without some clinical evidence that HD is active in that patient. Accordingly, the evidence of clinical activity should precede the time of death by, anywhere from a few weeks to several years. If the patient with HD has been treated apparently successfully and never again develops a clinical manifestation of disease, then it is going to be very difficult for him to die of HD. This is a very simple-minded logical approach and accordingly I began to look for data on this point, namely, the time interval in months between the first course of treatment and the first new manifestation of disease.

Initially I found that such data are very fragmentary. In the world's literature, there were only a handful of reports. This is sad and surprizing when one considers how many Institutions around the world have such data in their files. One point I would like to interject here to our very dear host, Dr. Santos Silva, is that perhaps one of your young men here, at this Institution, where you have many cases in your files, could perhaps help us in this way, by searching your own records for this kind of information. What is needed is to record either in your own cases that have been treated here, and followed entirely here, or in cases that come to you from elsewhere, having been treated elsewhere, but these should be kept separately, the time interval from the first course of treatment until the first documented evidence of new disease, whether it's a lymph node or the development of fever which is later shown to be due to say bone marrow or liver involvement. I think that such data are of extreme importance and we need to get them from many parts of the world in order to know whether the little bit of data that I have been able to gather is valid and representative or not.

With that as a commentary I would like to show you just 2 slides to indicate the data that I have been able to collect to the present time from our own Institution. In addition to the material on the slides I might mention that the several case reports, approximately 6 case reports in the world's literature, in which this specific statistical information has been provided by various authors, indicates an average interval from the first treament to the first new manifestation of approximately 12 months.

Here you see the first of 2 slides. In this slide I have tabulated the data for all patients with Stage I and II disease that we have treated on the linear accelerator, during the past 10 years or so in which there had been no previous treatment of any kind. This is again the interval to the first new manifestation of disease in months.

The cases have been shown classified by the time at risk. Obviously patients treated only during the last year could not demonstrate a new manifestation 5 years later because they haven't been followed that long. You'll notice that total count at the bottom shows that there were 109 cases avai-

lable for this analysis. Sixty-nine, or 62.12% of these patients have never, at any time, demonstrated a new manifestation of disease. Four patients have died of intercurrent disease without evidence of HD. Forty patients, or 47%, have at some later time, shown a new manifestation of disease. You'll notice that of those who have, out the 40 with new disease, 15 occurred during the first 6 months, after treatment was completed, 8 more during the next 6 months, altogether 57% of the new disease occured during the first year. In 10 additional ones during the second year, so that altogether 82% of the new instances of disease occured during the first 2 years. This is in a remarkably good agreement with an earlier, very crude estimation that I have made from our own data and that in the literature, which suggested that 85% of all new manifestations will occur by the end of 24 months after treatment.

Notice that in this particular study there were, of course, very few cases that had an opportunity to go longer than 5 years, only 26 were at risk, and there were none of these that showed new evidence of disease after the fifth year. In this particular group there was none after the fourth year. In any case it should be clear that the new disease is very strikingly expressed during the first 2 years, and becomes much less frequent thereafter and is extremely infrequent after the fifth year.

One could say: this is a selected group of cases and perhaps they have been selected in such a way as to reveal a biased distribution on this particular statistical manifestation. However I have now looked into another group of cases in which this criticism is not valid. These are patients who were first treated in some other Institution and they have come to us with new disease at some later date. If there are indeed many many cases of HD that are treated elsewhere perhaps who develop their new disease not during the first 2 years, but perhaps in the 5th year after treatment, or the 15th year, then surely, at random, we should see a reasonable sample of such cases in the patients that come to us since there is no obvious selection factor to bring only the early recurrences to us for additional treatment.

In this slide you see an analysis of 60 cases in which treatment was first started at some other Institution, and the time at risk, anywhere from a few months to over 10 years, as indicated on the slide and you can see that there is only one case with a new manifestation occuring after the fifth year, in the eighth year. All of the remaining cases occurred in less than 5 years, and 90% of these were during the first 2 years.

I think that this other data, at least to me, seems to be rather convincing evidence that the time course of new evidence of disease is not randomly distributed, does not have an equal chance of occurring 5 or 10 or 15 years later, but is indeed extremely concentrated during the first 2 years, and to a lesser extent, during the first 5 years.

The data strongly suggests that if a group of 100 patients were to survive 5 years beyond the original course of treatment, one could be confident that at least 95 of those 100, and perhaps as many as 99 out of those 100, would indeed be permanently cured.

The final point I would like to make is just a brief recapitulation of what I think the prognosis might be with optimal technique in those Stages at the present time.

I stress that this has to be stated with some caution because my own data and those of Dr. Peters using the most recently devised techniques and using lymphangiography, relate still to a rather small number of cases. It will be necessary to extend such studies very considerably, not only in our own Institutions but in many other Institutions before we can be sure that the figures that have emerged up to this time are valid and representative figures. Nonetheless I would say that, optimally, it should be possible to offer permanent cure to patients in Stage-I in at least 85 to 90% of all cases. I think it should be possible to offer permanent cure to patients in Stage-II in approximately 70 to 80% of all cases, but here there will probably be a sharp distinction beginning to emerge between patients in Stage II-A and those in II-B, and I do not yet have enough data to give me

any reasonable impression of what the difference in prognosis will be, except that I am sure that there will be some difference in prognosis between the A and the B groups.

In Stage-III the statement must be made even more cautiously because, as you saw yesterday the data are extremely limited in addition to the protocol series of 19 radically treated cases that were on the slide I showed you yesterday I have approximately another 30 cases, nearly 50 cases altogether, that have been treated radically with demonstrated Stage-III disease. And of those the indications are that the overall survival free of disease for more than 2 years, and that is based on the data you just saw, one can hope that a 2 year survival cure of disease, will at least give some rough measure of potencial curability. The survival free of disease for more than 2 years is approximately 60% in the entire group. My best estimate is that Stage III-A will turn out to be rather close, surprizingly close, to Stage II-A. Indeed I think that we may find that the curability of patients in Stage-III, if they have no constitutional symptoms, is better than that of patients Stage-II who do have constitutional symptoms.

The prognosis in Stage III-B is appreciably worse largely because many patients who appear to be in Stage III-B, on careful diagnostic evaluation, will, in fact, turn out later to have silent disease in the bone marrow, the liver, the lung or some other Stage IV site, which could not be detected at the time of the initial study because of the limitations of our present diagnostic techniques. So that I would predict that the optimal survival in Stage III-B, with our present techniques will probably not be much better than 30%.

In Stage-IV we still have no good estimates, but as I mentioned the other day, Stage IV is a very heterogeneous group of cases, and there are some patients with localized disease in the lung or in the subcutaneous tissue or even in the pleura, who are curable despite the presence of Stage-IV disease.

The chances are that these will comprise no more than 10 or 15% of Stage-IV, and Stage-IV, at least in our experience, is a rather infrequent group, in HD. It is very difficult, at this time, to give any realistic estimate of curability. I simply want to make the point that even in Stage-IV there may be some cases that have chances for cure. They must be selected carefully. Certainly those with widespread bone marrow involvement are beyond the hope of cure by our present techniques.

Altogether, if one adds up the various proportions of Stages that we have found thus far, and if the proportions of Stages that we see are valid, that is, if they are representative, one might project an overall cure rate for HD. of somewhere beetween 50 and 70% as being possible, with the radiotherapeutic techniques that we have at our disposal at this moment.

Dr. Vera Peters :

I would like to merely confirm what Dr. Kaplan has told you so far, and add some evidence in the slides about to be projected.

The first slide demonstrates the flattening of the survival curve after 10 years even in the past experience. From 10 to 30 years, the survival curve in the overall picture is paralel to the survival curve of the normal population of equal age and sex distribution. Unfortunately I haven't demonstrated this by adding the survival curve, but I have worked it out at various times and I can say that it is fairly parallel with the experience in the central plotted line which gives the overall picture from 10 to 30 years.

The diversion after 25 years is merely because this represents a very small number of patients, I believe it was around 30 patients followed after 25 years.

Looking to the future, as suggested by Dr. Kaplan, this curve should present the same conformation but should be higher and the curve of Stages II-B and III should be slightly higher, but this remains to be seen.

The next slide gives the actual survival rate at 5, 10, 15, 20, 25 and 30 years in the past experience. Referring to the 10 year survival it is of interest that out of 358 patients we have now 100 who have survived

10 years or more, making an overall 10 year survival rate of 28%.

The next slide presents the medium survival according to the stage of the disease but using the old-staging, and will not apply exactly to the present clinical classification. In Stages I and II-A the median survival is somewhere between 10 and 12 years. Beyond that, in the later Stages the median survival is somewhere between 9 months and 3 years, if you group them according to early and late. This should be much higher and I'm not sure whether this will change but certainly the median for the later stages should rise somewhat in the future.

The next slide presents the data of actual causes of death amongst the patients who survived more than 10 years and who, in addition, had a 10 years freedom of disease interval. Some of them up to 25, 30 years. None of these patients died of HD. Actually the patients after being followed for 10, 15 or 20 or 25 years, enter the age group where cancer is more common than HD. Note that quite a few of these died of other cancers. One cancer of the cervix, 2 cancers of the bronchus, 1 carcinoma of the stomach, 4 of these died of other cancers, but none developed other lymphomas. We had in addition one other who died of extraneous disease at 8 years, who died of leukemia, I think I mentioned this one before.

This slide shows how we plotted out the effect of treatment on the 5 and 10 year survival. The top line is 124 cases who had a high tumor dose to the involvement and, in addition, received some treatment beyond the involvement to the adjoining lymphatic regions but, in our past experience this treatment was not of a high enough dose to avoid recurrent disease in a certain percentage. The lowest line is the survival curve of those who received a low tumor dose to the involvement and who did not receive any irradiation beyond the sites of involvement. The other 2 speak for themselves, the second line received a high tumor dose to the involvement but did not receive any irradiation beyond the involvement. The 3rd. line is the survival curve of those who received low doses to all the lymphatic regions, but did not receive adequate treatment to any of the sites of involvement.

This is merely the evidence in the past experience of curability and the possibility that this will improve.

Dr. John Ultmann :

I would like to second the previous 2 positions that certain patients with HD are curable. I should also like to draw your attention for a moment to another way of looking at this so that we can see the whole perspective of what remains to be done. I'll do this extremely briefly.

Step 1 — I think ideally we would try and identify the etiologic agent of HD. I think that we are far from this and I don't think that the patients can wait for us to identify the agent and further more if tuberculosis, for example, is taken as a disease in which the agent has long been identified I think we will all agree that social factors, genetic factors and still other unknown factors would remain to be worked out for HD, after the agent is identified. In this regard I would only like to mention what Dr. Aisenberg has already brought up, and that is that when we have identified the agent that does cause HD we will have to face the problem of not only erradicating overt disease but preventing re-infection if there were such a thing. At the moment I think, as far as Step I is concerned, we are quite far removed from this ideal situation.

As far as Step 2 is concerned I believe that the most important thing in promoting curability of HD is to identify the patients with local HD. Although it is true that Dr. Peters data which she reported a number of years ago, and which we have already mentionated, that these data indicate that the patient who has the longest illness preceding appearence at the radiotherapy center may have the best prognosis because of indolent disease, it seems to me reasonable to assume that it might be useful to identify all patients early and still do better. How one can do this? I leave it to your own devices, education, alertness on the part of the physician, all this will be helpful. In this regard the third Step in improving curabitity would be to alert the physician who is fortunate enough to see a patient

with one node, not to pass it up for a long period of time and just keep an eye on it, or watch it. That is, I think, a detriment to the curability of this disease.

As has already been mentioned, I believe that curability comes from the appropriate treatment, depending upon your own personal facilities, either of the local disease, with the ports that have been mentioned, or eventually of extended radiotherapy.

I think we tried to imply this morning that some progress in development of additional systemic agents will also add to the curability as defined by Dr. Kaplan, that is to say, not necessarily complete erradication of the disease but its control so that the survival of the patients approximates that of the cohort of his age group.

This was all the comment I wanted to make, Mr. Chairman, except if you permit me, since we did skip the role of surgery I thought I'd take one or two minutes to say a word on that.

You may have noticed, I don't know if the members of the audience received the first circular. This first circular had a section entitled: The role of surgery in the treatment of HD. If you look at your program now it has been modified to the role of surgery in the treatment of HD as seen by the non-surgeon. I think that is fair because all of us here at the table are non-surgeons I believe from previous experience with the Panel that we all agreed on the following: surgery as the definitive treatment of Stage I HD has no advantage, whatsoever, over aggressive radiotherapy as outlined by Drs. Kaplan and Peters.

All the patients in the literature, or almost all who have had surgery with intent to cure, have had further radiotherapy with the intent to cure a little better. Since the surgeon is incapable of knowing that he has removed that last lymph node, and since he makes it a little more difficult for the radiotherapist to do the very best job, most of us feel that the treatment of choice does not lie in this area.

Since I firmly believe that I must maintain my friedship with the surgeons, I'd like to just show you that there are plenty of things to do for the surgeon. Furthermore you'll have to have a surgical friend who will help you make the diagnosis of the disease. The surgeon most often will help you with the lymph node biopsy. He may have to biopsy other areas and you can encourage him to do so rather than to treat without a histologic diagnosis. He will be glad to assist you with thoracotomies and laparotomies to make the diagnosis. He may have to assist you in emergencies with laminectomy and establish at the same time the diagnosis.

The second portion of the slide shows you that in the course of the treatment of a patient with HD the surgeon may have plenty to do. If you encourage him that there are things he can do he may not want to cure the patient, he may want to help you to keep the patient well. Amongst the things that he can do for most is the patient who has less than 24 hours onset spinal cord syndrome, in whom the advance of the disease is extremely rapid. The patient may be better off to have a laminectomy followed by radiotherapy than to have radiotherapy alone.

The patients may have obstruction in the gastro-intestinal tract or urinary tract, or hemorrage from the gastro-intestinal tract in which there is some usefulness for surgery, of course. I'll come back in one minute to splenectomy. There is a role for control of pain in the patient who is severely incapacitated and may need a chordotomy or rizotomy or something in that neighborhood.

Obviously with Dr. Kaplan and Dr. Peters placing patients into categories where they will have a normal survival time as of their cohort, opens large vistas for the surgeon, namely, many unrelated conditions will occur and he can take care of this, of course, and should take care of them, and never should the internist or the surgeon assume that it is HD that is causing a new symptom. It, more likely than not, after the second or third year, is appendicitis, cholecystitis, adhesions, or what you will, or a new cancer even.

The next slide summarizes the indication for splenectomy. Occasionally when the hemolytic anemia or the thrombocytopenia, or the leukopenia can be demonstrated by the appropriate isotope studies, or by other

means, to be due to hypersplenism, it may be useful to remove the spleen.

The next slide, borrowed from Grace and Mittleman, in Buffalo, Roswell Park, indicates the experience in 5 patients, who had a red cell survival done before and after splenectomy. Before splenectomy the half-life was 11 days and after splenectomy it was normal. However I wish to remind you, if you look at their paper, that splenectomy carries a greater morbidity in HD than, let us say in Laennec cirrhosis or in post-traumatic splenectomy.

Finally I can't help but close reminding you once more that it can be quoted from the article by Grace and Mittleman that: "it is our opinion," they say, "that the role of surgery in the overall management of HD is limited to the excision for diagnostic purposes and to the management of unrelated problems which might require surgical intervention.'" This, I believe, is the considered juldgement of most surgeons and, I think, the considered judgement of all radiotherapists and internists. (*)

Dr. David Karnofsky:

It is unfortunate that I have to be last in this group because I am not sure of the term "cure", although Dr. Kaplan has a definition for it. That does not necessarily mean that his definition is applicable to HD.

I think we like to use the word, as a matter of fact will be using the word, because I like to think that we do cure patients with HD, but nevertheless, in order to maintain a perspective on the disease and fill in the gaps that Dr. Ultmann mentioned, I think we have to avoid the use of such a definitive term. For example in tuberculosis, do we cure tuberculosis with chemotherapy? The answer is no because one may still find foci of tubercle bacilli and these may actually rise up again many years later under certain conditions. Then I think we think in terms of cure when these patients are controlled for long periods of time. Or if one gives insulin in diabetes the patient is controlled, we don't cure the disease but we come pretty close to eliminating many of the immediate complications of the disease by insulin. So I would much prefer the use of the term "control" of HD. Also even in those patients that don't fall under the category of cure by virtue of the fact that they don't recur say, after they are free of disease for a 5 year interval after treatment. There are many patients with HD who do have reccurrent disease. They are not cured, by any definition, yet they may work for 15 or 20 years requiring intermittent courses of treatment.

The Panel may want to go into more details exactly what it is meant by cure. A second consideration I think we have to face in discussing the term "cure". I think everyone is thinking of "cure" in relation to the effects of treatment. We have to accept the fact however that there have been patients with HD who had minimal treatment and have apparently been free of disease for many years. This is what Dr. Kaplan calls the unitotal method, but on the other hand it is still true and it indicates that there is a variation to the disease. So one can say that HD by the definition advanced, is curable even without very effective treatment. I mentioned the case yesterday of a patient who went into spontaneous regression for an unexplained reason and he apparently is cured.

I think the big question that we are trying to decide here really is: Is cure dependent on the administration of a particular form of treatment? I think yesterday I outlined the reasons for accepting intensive and extended radiotherapy as the most reasonable and effective form of treatment of HD. I agree with Drs. Kaplan and Peters that one must proceed on this basis, to treat our patients and I believe that they are correct. I'm not trying to minimize their contribution or the fact that this is the best present method of approaching the problem of HD.

I think one must keep an open mind until the data are conclusive that there is a positive correlation between the intensity and precision of therapy in suitable cases and the number of patients who live long enough, to die of unrelated causes the same as their cohorts in the population.

---

* Ver página ... dêste Simpósio.

Dr. Joseph Burchenal:

Despite the fact that occasional spontaneous regressions occur, and sometimes people get better without perhaps what we do consider adequate therapy, you still feel that this massive intensive therapy should be used?

Dr. David Karnofsky:

I don't think there is any doubt that patients have lived longer and had longer periods free of disease, but I think it's the intellectual objection to the meaning of the term "cure", which may confuse our understanding of the disease.

Dr. Joseph Burchenal:

It's more an intellectual than a private hope?

Dr. David Karnofsky: Yes.

Dr. Henry Kaplan:

Dr. Karnofsky does not accept the definition of cure that I gave but the critical analysis that I presented as an indication of possible cure. I think it is fair to call on him for his own definition of the word "cure". As opposed to control what would you accept as a cure?

Dr. David Karnofsky:

Well I think as has been suggested already that the definition of the term of cure of HD ultimately may be dependent on the identification of the patho-physiology of the disease or the defect in the cells that are responsible for the disease and some method of demonstrating conclusively that there is no longer any evidence of this process, or the systemic disturbance, that may help the disease to exist in the individual. And this I realize is a very fanciful argument because you don't have these tools at the moment but I think there's no objection to waiting as long as your patients feel well and survive indefinitely.

Dr. John Ultmann:

I think it is wonderful to end a factual Symposium on philosophical notes. I think it's very appropriate and since you're all fatigued, you can sort of not fight back this impulse we have to be philosophical. I will side with both Dr. Kaplan's definition and Dr. Karnofsky's. I've already mentioned personally that I agree with Dr. Karnofsky that there are many things still missing till we can speak of cure in the intelectual sense of the word. We have to understand, we have to fulfill certain postulates and so on. But on the emotional and educational side I'm afraid I must completely agree with Dr. Kaplan. I would like to reiterate this point for the following reason. Since the past few years, since Drs. Kaplan and Easson and Peters and others, have aggressively asked the medical profession the question: "Can HD be cured?" the profession has responded by examining its activities in an attempt to cure HD. That is to say, they have at last questioned the relevance of giving small doses of treatment. I think that, although intelectually I'm completely with Dr. Karnofsky, I think it would be a mistake if you went away and we broke down this wonderful concept which actually is going to bear direct benefit to the patient, namely certain patients with HD, treated a certain way can be cured. Let's cure them. Other patients, unfortunately cannot, but that's another subject.

Dr. Joseph Burchenal:

There have been certain chemotherapists who claimed that the reason chemotherapy gets such poor results is because it is used in Stage III and Stage IV disease. And that if they could only treat the early Stage I disease that they could get much better results. I believe the group in Russia have done some of this. Dr. Kaplan would you care to make any comments about the use of chemotherapy early, in place of radiation therapy?

Dr. Henry Kaplan:

At the time of the Rye Conference the only data that we could find in any one series were those that Dr. Wintrobe had at Salt Lake City and because Dr. Wintrobe was ill at that time it was not possible for him to pull out the data from his files to establish just how good this treatment really is. But to my knowledge that's the only significance there is in which reported Stage

I and II cases have been treated in this way. It's fair to say that none of those patients did have lymphangiograms, so it's probably unfair even to Dr. Wintrobe to analyze them since even he doesnt know whether they were Stage I or Stage II disease. Indeed we are in a curious situation of having to do our work over again in the post-lymphangiogram era because a great deal of the data that has been published in the past, prior to the general use of lymphangiography is no longer valid in the light of what we now know about the diagnostic inaccuracy of such data.

I will mention in this conection, for example, the paper by Shear from Memorial Hospital, on the spread of reported Stage I disease. I cannot say that it is not true but I can say that he does not know if it is true or not, because none of those cases had lymphangiograms.

Dr. Joseph Burchenal:

The reason I brought this question up is that from animal experimentation we know that the smaller the tumor the better the results with chemotherapy. I believe that the Russians' results, and I gather that Dr. Wintrobe's results also were better on Stage I and II than they were on far advanced disease. That's to be expected. The point that I would like to bring out is that these are just relatively slightly better, whereas the things that Dr. Kaplan and Dr. Peters are talking about patients where the disease goes away and does not come back, not for just a year, or 6 months or something like that. They remain free of their disease for many many years, and are presumably cured. It seems to me that chemotherapy in Stage I or II is absolutely contra-indicated, unless it might be given as an adjuvant to intensive radiation therapy, but it should in no way take the place of radiation therapy.

Dr. Vera Peters:

I just wanted to mention one other philosophical aspect of cure versus control. I think it is very important that we continue to use the word "cure" and we can always modify it by calling it apparent cures, because it gives the patient hope. The patients are young and they are very active, they all want to know how long they could live and they want to know whether they should have families. All these things are so important to the potentially curable patient — here I am using it again — but I think we should get the cure habit in order to give the patients hope, because it has a tremendous effect on their attitude and on the way they accept their responsabilities after treatment and later.

Dr. Henry Kaplan:

I agree with Dr. Peters about the emotional importance of being able to use the word cure if there's any reasonable basis for doing so and I think we have presented the evidence that there is a reasonable basis.

I will also point out that while we are on the rebuttal from Dr. Karnofsky, that waiting for an understanding of the etiology and pathogenesis of the disease before we can invoke true cure, may be like looking for the pot of gold at the end of the rainbow. Dr. Ultmann has already mentioned that in one disease, namely tuberculosis, where we do know the cause, and we know many of the factors we have not really achieved a cure. We can easily point to a number of kinds of cancer where cure rates are now reasonably well established, where the tumors are under direct vision, that is we can see them either in the eye or on the skin and where there's freedom from the cancer for many many years, it is well documented and we can speak of cure even though we do not know the cause of either cancer of the skin or retinoblastoma. Therefore I don't see the compelling logic of having to understand the etiology of HD in order to speak of cure, if we are prepared to accept the concept of cure for any other disease for which we do not yet know the etiology.

Dr. David Karnofsky:

In self-defense I can say that I also use the word cure and I think that I've said earlier that I have no objection to the term. I think it can be a sterilizing term, not just in HD but also of our understanding of the process and I don't believe I said we have to understand the etiology to employ the term "cure". If you have some basis for

demonstrating whatever the pathogenesis or problem produced by some biochemical disturbance produced by the disease, if there is an inderlying disturbance that it has been eliminated. In the case of retinoblastoma, as Dr. Kaplan points out, it is a local problem and when the tumor is destroyed apparently it does not recur. That may be true of localized HD, but there's evidence to suggest that it may not be, and this is really the area we're talking about. I will concede for practical purposes, in patient management, and in encouraging physicians to treat their patients properly, aggressively, adequately, that this Panel should agree that HD can be cured.

Dr. Henry S. Kaplan

In addition to the well-known criterion of cure formulated by Easson and Russel (1), other evidence is now available to support the view that permanent cure of Hodgkin's disease can indeed be achieved. A number of patients have died of intercurrent disease several years after treatment for Hodgkin's disease and have revealed no evidence of Hodgkin's disease at postmortem examination. If macroscopic disease were still present in clinically quiescent form in such instances, it should have been detectable at autopsy.

Secondly, I have previously called attention to the fact that new manifestations of Hodgkin's disease are not randomly distributed in time, but tend to occur predominantly within the first two years after the initial course of treatment and decrease in frequency rapidly thereafter to become quite rare after the fifth year. A more recent analysis of our data will be presented to document this point more conclusively. Two groups of cases have been analyzed: (a) previously untreated patients with Stage I and Stage II Hodgkin's disease, who have received radical radiotherapy at Stanford Medical Center; and (b) patients previously treated elsewhere, who have come to Stanford Medical Center with new disease activity requiring treatment. In both series, it was found that between 80 and 90 per cent of the new clinical manifestations occurred within the first two years after the initial course of treatment, and only one case was encountered in which the first new manifestation of disease occurred after the fifth year. It should be clear, therefore, that a patient who has remained well for five years after an initial course of treatment has a very great chance, on the order of 95 to 99 per cent, of being permanently cured.

REFERENCE

1 — EASSON, E. C., and RUSSELL, M. H. The Cure of Hodgkin's Disease. *Brit. Med. J.* 5347: 1704-1707, 1963.

THE OVER-ALL PLANNING OF THE TREATMENT OF THE HODGKIN'S DISEASE PATIENT*

JOHN E. ULTMANN

The management of patients with Hodgkin's disease requires understanding of the natural history of the disease, familiarty with the therapeutic modalities, patience, and sympathy. As soon as the histologic diagnosis has been established, it is wise to formulate a long-range therapeutic plan that not only encompasses the immediate problems but anticipates those likely to arise during the evolution of the disease. If the disease is localized, i.e., Stages I and II and particularly II-A, the patient should be referred to a radiotherapist for a course of intensive, curative radiotherapy with supervoltage radiation. An attempt at curative radiotherapy should be made regardless of the histologic type revealed by biopsy. The delivery of high doses of radiant energy is a highly specialized field and is best carried out in those centers that have the greatest experience. As has been stressed by others, a number of investigators have accumulated evidence which has shown that radiotherapy directed not only to the original tumor but also to contiguous areas no clinically involved significantly improves survival statistics. Thus, Peters and her associates, Easson, and others have shown that radiation to the adjoining lymphatics of Stages I and II-A improves survival from a 5-year survival of less than 60% of the patients to a 5-year survival of over 70% of the patients. The results with radiation therapy for Stage II-B, the symptomatic regional disease, and for Stage III are not so favorable-less than 20% of patients suriving for 5 years. Kaplan has demonstrated that the recurrence in previously treated areas of Hodgkin's disease is related to the inadequacy of dosage delivered to that particular area. Thus he has calculated that the recurrence rate is decreased to 10% or less if over 3000 rad are delivered to a field involved with Hodgkin's disease. A few years ago, Kaplan embarked upon a more aggressive approach to the treatment of Stage I or Stage II-A Hodgkin's disease, that is disease confined to lymph nodes above **or** below the diaphragm, or the spleen, or Waldeyer's ring. Advocating that the involved areas as well as **all** lymph node-bearing areas should be treated, Kaplan has accumulated statistics for Stages I and II cases which appear to be superior to those reported by others whose efforts at radiotherapy are more restricted. Thus, he has increased the 5 year survival rate from 70% to over 80% with his techniques. In addition,

* Resumo da conferência.

based upon his experience with these cases, Kaplan has embarked upon a course of treatment for Stage III disease, that is extensive lymphoid involvemente above **and** below the diaphragm, including, at times, the spleen. A preliminary report from his series indicates that his results may be superior to those achieved with any currently available chemotherapeutic agents.

For the patient with symptomatic regional dissease, that is Stage II-B, or those with disseminated disease, Stages III and IV, an entirely different approach would generally be used. The majority of these patients will be given systemic chemotherapy. Nitrogen mustard was the first alkylating agent to be employed. It serves as a reference for the new agents which have since been developed. Nitrogen mustard, Mustargen®, is administered intravenously; usually a total dose of 0,4 mg/kg is delivered as a single dose, occasionaly it is divided into 2 to 4 daily doses. The toxicity locally, the nausea and vomiting, and the eventual depressing effect on the bone marrow are well recognized and can be prevented by judicious selection of the dose, meticulous intravenous administration, and by premedication of the patient with barbiturates and chlorpromazine. When nitrogen mustard was the only agent available, it was given intermittently whenever an exacerbation occurred. In previously untreated patients with systemic disease, one can expect a remission lasting 2 to 8 months in 60 to 80% of cases. With the appearance of orally administered alkylating agents, such as chlorambucil, it has become customary to induce remissions with nitrogen mustard and maintain these with the oral alkylating agent. A comparison of over a hundred cases by Frei and Gamble indicated the usefulness of maintaining nitrogen mustard-induced remissions with chlorambucil. Whereas only 50% of patients remained in remission 10 weeks after nitrogen mustard alone, more than 50% of patients remained in remission 40 weeks after nitrogen mustard therapy followed by chlorambucil maintance. Because of the unpleasant complications of nitrogen mustard administration, cyclophosphamide (Cytoxan®, Endoxan®) has been advocated in those instances where immediate results are not necessary. Following induction of remission, usually by the intravenous route, the remission so obtained is continued by the administration of oral cyclophosphamide. In addition to the toxicity mentioned under nitrogen mustard, alopecia and hemorrhagic cystitis may occur; the alopecia is reversible when the dosage of the agent is reduced.

For the past four years, a derivative of the periwinkle plant has been available. Vinblastine sulfate is an alkaloid derivative closely related to vincristine. Vinblastine is usually administered intravenously; however, an oral preparation has received preliminary trial. For the intravenous route, 0.15 mg/kg is usually given initially and this is increased by .05 mg/kg every week, until .25 mg/kg per week is reached. It is then continued at weekly intervals, until there is tumor regression or a change in the blood count or other toxicity. The majority of the toxic manifestations are readily reversible when the dosage is reduced. We have studied 16 patients all of whom have had advanced Hodgkin's disease: 3 patients had extensive radiotherapy; two had alkylating agents; and 10 had received alkylating agents **and** radiotherapy. One patient had failed with methylhydrazine. These sixteen patients were given 17 courses of vinblastine. Three failed to respond and in one the response is uncertain. In the other thirteen courses, however, significant objective improvement occurred. The objective improvement consisted of reduction of fever, lymph nodes, hepatomegaly, splenomegaly, and sedimentation rate and an increase of weight, performance status, and hemoglobin. The mean remission duration, maintained by intravenous vinblastine, was 10 months. One representative patient, who had failed to respond to two alkylating agents and to 6-mercaptopurine at another institution, appeared at our hospital with weight loss and systemic manifestations as well as lymphadenopathy. With vinblastine it was possible to induce and maintain the remission characterized by a decrease in fever, lymphadenopathy, and malaise and an increase in hemoglobin and in weight. The patient is still in remission.

A number of complications of vinblastine therapy have been reported in the literature. These include: leukopenia, thrombocytopenia, nausea and vomiting, abdominal colic, and constipation, occasionally termi-

nating in ileus. Alopecia may occur. Paresthesias, alteration of taste, general, weakness, malaise, and depression have been reported. Occasionally, patients report pain in the affected lymph nodes. The majority of these toxic manifestations are reversible and improve when the next injection is omitted or the dosage decreased.

Recently, Bond **et al.** summarized their results with a new, improved oral vinblastine preparation. Seven of 12 patients with Hodgin's disease had an excellent or a good response. The toxic manifestations were not dissimilar from those seen with intravenous vinblastine and usually could be controlled with concomitant administration of chlorpromazine. Carbone **et al.**, using intravenous vinblastine, have obtained results which suggest that it may be a better agent for initial chemotherapy than the alkylating agents.

Approximately three years ago, a new class of agents — the methylhydrazine derivates — became available. N-isopropyl-a-(2-methylhydrazine) - p-toluamide HCl, ibenzmethyzin HCl (Natulan® is the methylhydrazine derivative most commonly used at the present time. This compound does not have cross resistance with the other cytotoxic agents. It has been shown to fragment DNA **in vitro**, probably as a result of the auto-oxidation with peroxide or by hydroxyl radical formation. The compound is administered orally, usually starting with a dosage of 50 mg per day and increasing the dosage over the next few days to 300 mg/day. At this level, the MIH is continued until the appearance of tumor regression or toxicity. The average loading dose in our series was 9.0 gm given over 50 days. The maintenance dosage ranged from 50 to 150 mg/day We have adminstered methylhydrazine to 9 patients, all having advanced Hodgkin's disease. All 9 of the patients had failed on radiotherapy and alkylating agents, and, in fact, 7 had failed on the previously discussed vinblastine sulfate study. All 9 of the patientes showed objective improvement. This objective improvement was manifest by reduction of fever, lymph node enlargement, hepatomegaly and splenomegaly, and by increase in weight and performance status, as well as a rise in hemoglobin. The mean remission duration with methylhydrazine was 5 months. Matté, in a large series, has summarized his results with treatment of patients with vinblastine or methylhydrazine and reported approximately a similar remission rate.

A few of the patients with Stage III disease coming to special radiotherapy research centers are given extensive radiation treatment in an attempt to achieve longer remissions and longer survival than has been possible with the chemotherapeutic programs just outlined. Other patients, coming to special chemotherapy study centers, have been given combination chemoterapy to increase the per cent of patients going into remission and in an attempt to prolong remission duration. Combination chemotherapy is based on the fact that by reduction of dosage of each agent, the toxicity of each of these agents can be reduced, whereas the desired goals might still be achieved by the sum total effect of the drugs. The remission rate in patients given single agents, a combination of agents, and quadruple chemotherapy has been studied in an U. S. National Institutes of Health series by Frei **et al.** Although the series is small, it is readily apparent that major benefit may be derived in combination and quadruple chemotherapy, particularly in patients who have had **prior** treatment. The schedule empolyed in one such series of quadruple chemotherapy included cyclophosphamide, vincristine, methotrexate, and prednisone.

The adrenal cortical steroids have a limited but definite place in the management of patients with Hodgkin's disease. The constitutional symptoms can be relieved readily and this is particulary important in those patients who cannot tolerate radiotherapy or chemotherapy because of bone marrow depression. Toxic reactions to these potent steroids must be anticipated and prevented. Smaller doses of steroid are useful in the management of hemolytic anemia and of symptomatic thrombocytopenia.

Patients with anemia, who have become symtomatic, benefit from blood transfusions. No attempt is made to bring the hemoglobin level to normal.

When infections occur, the patient is given the appropriate antibiotic as determined from culture and sensitivity studies. It is not advisable to give prophylactic antibiotic therapy. When this is done, infections arise which are resistant to a large number of antibiotics. In patients with hypogammaglobulinemia, gamma globulin may be administered at regular intervals.

Hydration should be vigorous for patients with hyperuricemia as well as for those with hypercalcemia. Fluids may have to be administered intravenously in the early phases of treatment; later, oral intake must be encouraged and at least two to three liters daily should be given. If following vigorous hydration hyperuricemia persists, administration of allopurinol will prevent further accumulation of uric acid and will reduce the hazard of uric acid nephropathy in patients in whom rapid lysis of cells can be expected to occur following effective radiotherapy or chemotherapy. Allopurinol [4-hydroxypyrazolo(3,4-d)pyrimidine, Zyloprim®, HPP] is a potent inhibitor of xanthine oxidase and prevents the conversion of xanthine to hypoxanthine and of the latter to uric acid. Oral administration of 200 to 800 mg allopurinol daily to patients with lymphoma decreases serum uric acid and excretion of urine uric acid. There has been no evidence of renal, hematologic, gastrointestinal, or hepatic toxicity. In a few patients, attacks of gout have been precipitated in the early phase of allopurinol administration; this can ben prevented by prior administration of maintenance doses of colchicine. Drug dermatitis has occurred in a small number of cases

Control of pruritus in patients with Hodgkin's disease may pose a dificult or insoluble problem. Control of the underlying disease process offers the best method for obtaining relief of this distressing symptom. Other measures to control the pruritus include the antihistaminics, such as diphenylhydramine (Benadryl®), brompheniramine maleate (Dimetan®), or chlorpheniramine maleate (Chlortrimeton®),; sedatives, such as chloral hydrate or phenobarbital; and tranquilizing agents, such as chlorpromazine (Thorazine®).

The treatment of the lymphomas requires systematic analysis in order to provide the patient with the maximal opportunity for clinical cure or optimal palliation. The planning for therapy begins with a precise histological diagnosis. The staging of the disease after the oppropriate clinical, laboratory, and radiological studies have been made is then essential before deciding on the therapeutic regimen.

Radiotherapy is indicated for localized and regional disease regardless of the histological type. The treatment must be planned carefully and given in tumoricidal doses. In Stages I and II the first radiotherapy regimen offers the greatest opportunity for success. The internist shares with the radiotherapist the responsability of seeing that the treatment is well done. In Stage III disease there is a current experimental program of radiotherapy under investigation with the delivery of large doses of radiation to all lymph node-bearing areas and the spleen. It is to be emphasized that this is still a clinical research program and neither the long-term benefits nor the long-term hazards have as yet been assessed.

In symptomatic Stage III and Stage IV disease, chemotherapy is indicated. The antitumor drug armamentarium has been presented.

The inherent properties which will determine the rate of progress of the disease, as well as its susceptibility to treatment, cannot be precisely assessed when the patient is first seen. Until it is proved otherwise, the physician must therefore assume that appropriate therapy will suppress the tumor. It is well recognized that clinical cure is not always achieved, but research in progress in many laboratories throughout the world offers real promise for the future, perhaps within the lifetime of many of these patients.

SERVIÇO NACIONAL DE CÂNCER

INSTITUTO NACIONAL DE CÂNCER

DOENÇA DE HODGKIN

DISTRIBUIÇÃO POR GRUPO DE IDADE

1938 — 1965

GRUPOS DE IDADE	N.º DE CASOS	PERCENTUAIS
0-9	35	11.1
10-19	52	16.6
20-29	61	19.4
30-39	64	20.4
40-49	48	15.3
50-59	32	10.2
60-69	18	5.7
70 +	4	1.3
TOTAL	314	100.0

SERVIÇO NACIONAL DE CÂNCER

INSTITUTO NACIONAL DE CÂNCER

RIO DE JANEIRO —— BRASIL

1938 — 1965

TOTAL DE CASOS DE LINFOMA 954

TOTAL DE CASOS DE DOENÇA DE HODGKIN 314

PERCENTAGEM DE DOENÇA DE HODGKIN SÔBRE O TOTAL DE CASOS DE LINFOMA (ambos os sexos) 32.9%

PERCENTAGEM DE DOENÇA DE HODGKIN NO HOMEM SÔBRE O TOTAL DE CASOS DE DOENÇA DE HODGKIN 72.0%

PERCENTAGEM DE DOENÇA DE HODGKIN NA MULHER SÔBRE O TOTAL DE CASOS DE DOENÇA DE HODGKIN 28.0%

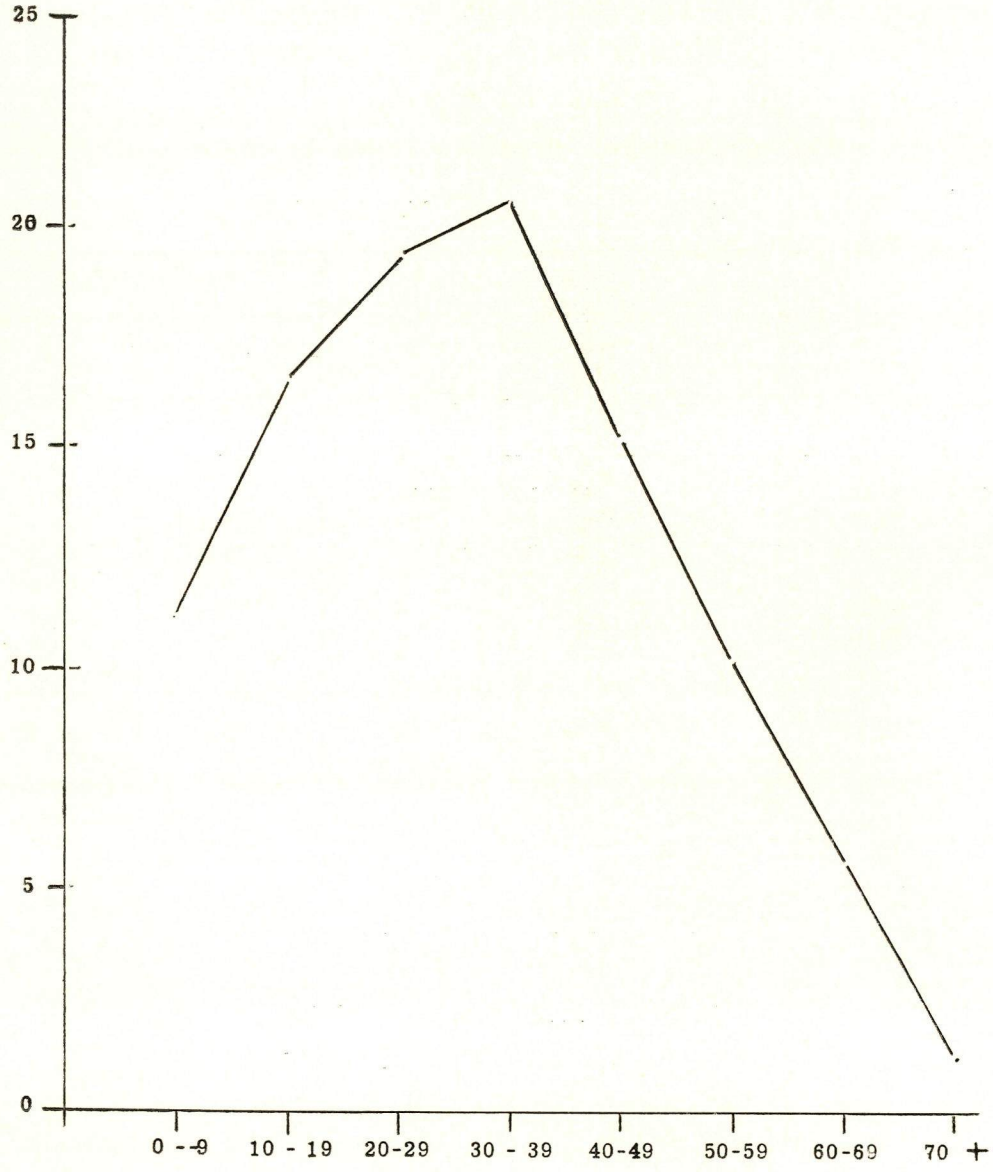


GRÁFICO I

DISTRIBUIÇÃO PERCENTUAL POR GRUPOS DE IDADE, DE CASOS DE DOENÇA DE HODGKIN REGISTRADOS NO INSTITUTO NACIONAL DE CÂNCER, NO PERÍODO DE 1938 - 1965

PERCENTUAIS

GRUPOS DE IDADE

SERVIÇO NACIONAL DE CÂNCER

INSTITUTO NACIONAL DE CÂNCER

DOENÇA DE HODGKIN

DISTRIBUIÇÃO POR SEXOS E GRUPOS DE IDADE

1938 — 1965

GRUPOS DE IDADE	N.ò DE CASOS		PERCENTUAIS	
	M	F	M	F
0-9	31	4	13.7	4.5
10-19	39	13	17.3	14.8
20-29	46	15	20.4	17.1
30-39	39	25	17.3	28.4
40-49	35	13	15.5	14.8
50-59	21	11	9.2	12.5
60-69	14	4	6.2	4.5
70 +	1	3	0.4	3.4
TOTAL	226	88	100.0	10.00

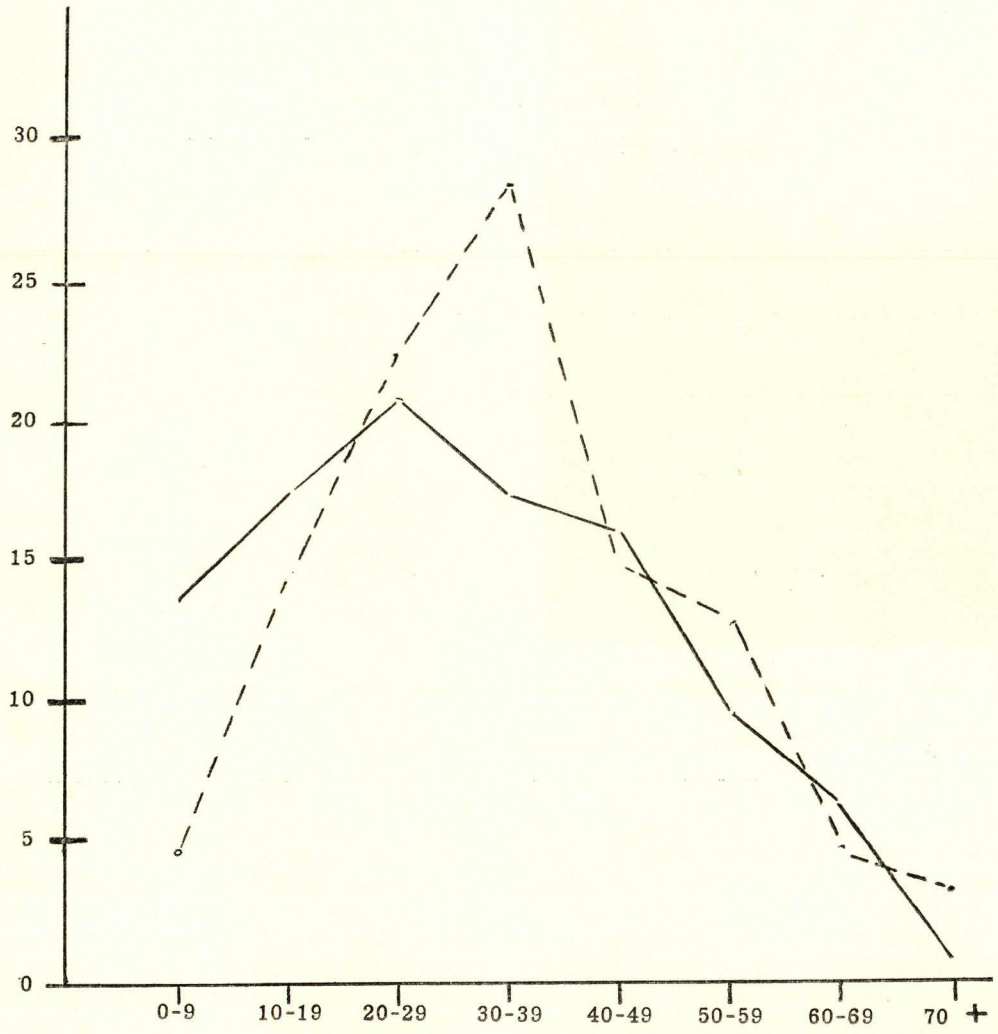


GRÁFICO II

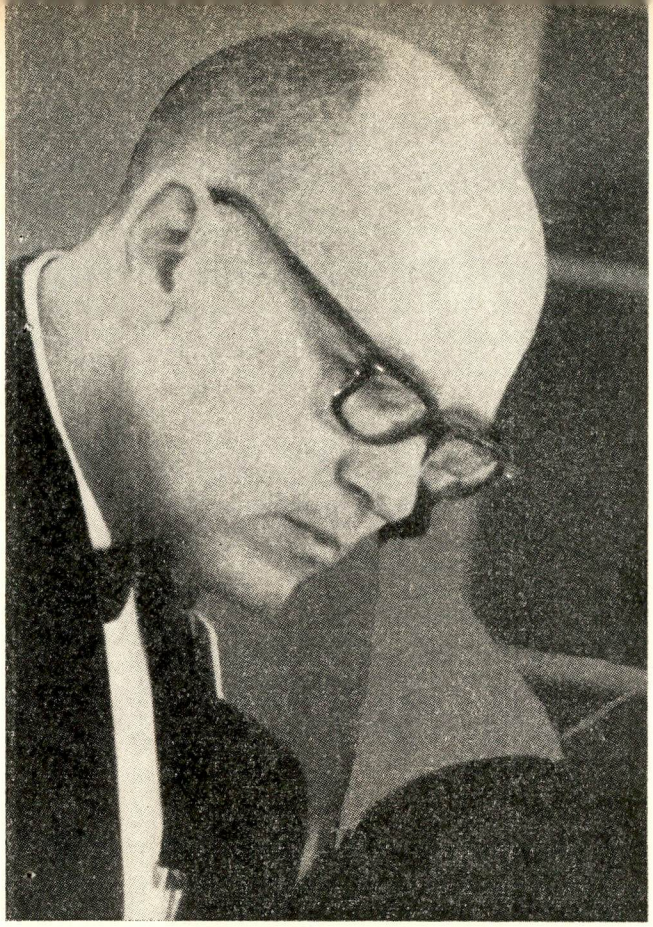
DISTRIBUIÇÃO PERCENTUAL, POR SEXOS E GRUPOS DE IDADE DE CASOS DE DOENÇA DE HOGKIN, REGISTRADOS NO INSTITUTO NACIONAL DE CÂNCER, NO PERÍODO DE 1938 - 1965

PERCENTUAIS

GRUPOS DE IDADE

HOMENS ————————

MULHERES — — — — —



UMA APRECIAÇÃO DO TUMOR DE BURKITT*

DR. JOSEPH H. BURCHENAL

A quimioterapia geográfica pode ser definida como o estudo das respostas aos quimioterápicos apresentada por tumores semelhantes que ocorrem em regiões geográficas diferentes. Tira partido da desigualdade da incidência de certos tumores em várias áreas geográficas, diferença essa presumìvelmente devida a fatôres ambientais ou genéticos: 1) para realizar a melhor quimioterapia possível no tratamento de vários tumores sensíveis, como o coriocarcinoma ou o tumor de Burkitt, que constituem sérios problemas em certos países; 2) para determinar se os tumores de aspecto anátomo-patológico semelhante em diversas regiões, respondem de maneira semelhante à quimioterapia. Se forem encontradas diferenças, pode sugerir-se que fatôres genéticos ou ambientais também afetam a resposta à quimioterapia.

O Dicionário Universal Oxford define um "stalking horse" como "um cavalo treinado para permitir que um mastim se esconda debaixo ou atrás dêle de modo a chegar bem perto da caça sem alarmá-la". Podemos dizer, por analogia, que o tumor de Burkitt pode servir de "stalking horse" em relação à leucemia, querendo com isso sugerir que o estudo cuidadoso do tumor de Burkitt pode desvendar o caminho para possível contrôle da leucemia aguda.

A maior parte dos dados que apresentarei provém da Conferência sôbre tumor de Burkitt que teve lugar em Kampala, Uganda, em janeiro de 1966, sob os auspícios da "Union Internationale Contre le Cancer".

O tumor de Burkitt é o tumor mais freqüente das crianças africanas e compreende mais da metade de todos os tumores que ocorrem em crianças em várias regiões (11, 16, 18, 38, 56). Tem sido encontrado também na Nova Guiné (80), Brasil (50), Colômbia (6), Índia (Desai, P. B. — comunicação pessoal), Inglaterra (Wright, D. H. — comunicação pessoal), e até mesmo, ocasionalmente, nos Estados Unidos (17, 58, 87). Na África constitui o tumor de Burkitt entidade clínica definida, diagnosticável

Êstes estudos foram patrocinados pelas seguintes bolsas: U.S.P.H.S, Research Contract SA-43-ph-2445, Cancer Chemoterapy National Service Center, National Cancer Institute, U.S.P.H.S. Research Grant CA-05826, National Cancer Institute; NCI Grant T 45, American Cancer Society, Delaware Division, e a Cambell Townsend Memorial Grant for Cancer Research from the American Cancer Society.

* O presente artigo é publicado com autorização especial de "Cancer Research", onde apareceu com o título: "Geographic chemotherapy-Burkitt's Tumor as a Stalking Horse for Leukemia". Cancer Research 12:2393-2405, 1966.

pelo quadro clínico, pela distribuição patológica (38, 56, 86), pela citologia (86) e pela microscopia com contraste de fase (70). O'Conor e Davies (56) classificaram histològicamente o tumor de Burkitt como um linfoma maligno do tipo linfocítico pouco diferenciado. Observaram êstes autores a presença de histiócitos grandes, de aparência espumosa, espalhados entre as células linfóides, dando ao tumor aspecto característico, denominado "céu estrelado". Wright (86) descreve as preparações citológicas do tipo "imprint", coradas pelo método de May Grunwald-Giemsa ou pelo método Wright, da seguinte maneira: (Fig. 1a). "As células linfóides têm 20 a 30 micra de diâmetro. Embora variem de tamanho, não variam no grau aparente de maturação. Seus núcleos são redondos, ovais ou bipartidos e têm um padrão de cromatina pontilhada. Os nucléolos são em número de 2 a 5, mas não são muito conspícuos nas preparações coradas pelo Giemsa. O citoplasma forma orla bem definida em tôrno do núcleo: é intensamente basófilo, com exceção de uma área mais clara, adjacente à indentação nuclear. Os vacúolos citoplasmáticos estão sempre presentes, em pelo menos algumas das células, porém seu número varia grandemente. Fragmentos destacados do citoplasma vacuolar (Fig. 1b) podem ser vistos usualmente entre as células linfóides". As figuras 2a, b. c, mostram células semelhantes da medula óssea de crianças do Memorial Hospital. Pulvertaft (70) acredita que os grânulos constituam o principal critério diagnósitco quando se usa a microscopia de fase. Êsses grânulos coram-se pelo ácido ósmico

Os tumores que se originam destas células apresentam-se nas mandíbulas e nas vísceras abdominais, poupando, relativamente, os gânglios linfáticos superficiais (12, 56). Os tumores de mandíbula são mais comuns em crianças de baixa idade. Onde a incidência é elevada, os tumores de mandíbula são freqüentes e a média de idades é relativamente baixa. Nos lugares em que a incidência é baixa, os tumores de mandíbula são menos freqüentes e a média de idades parece ser mais elevada (12). Isto se aplica particularmente aos casos encontrados na Europa e nos Estados Unidos, uma vez que, nesta base, seria de esperar uma baixa incidência de tumores de mandíbula. O tumor de Burkitt se restringe a nódulos localizados. Na África o acometimento generalizado da medula óssea é raro, embora tal não aconteça nos Estados Unidos (86). Êle ocorre por todo o Centro e Sudoeste da África. Parece ser dependente de certas condições de temperatura e umidade (85), exigindo temperatura anual mínima acima

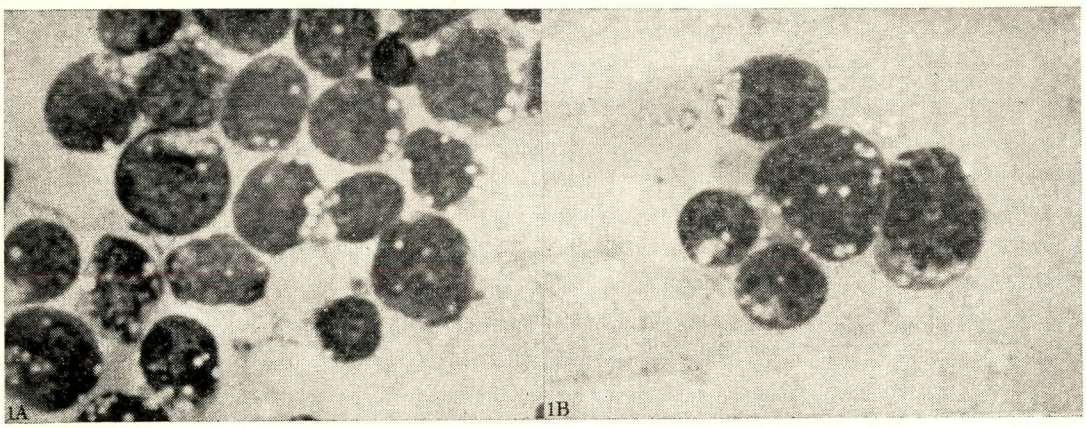
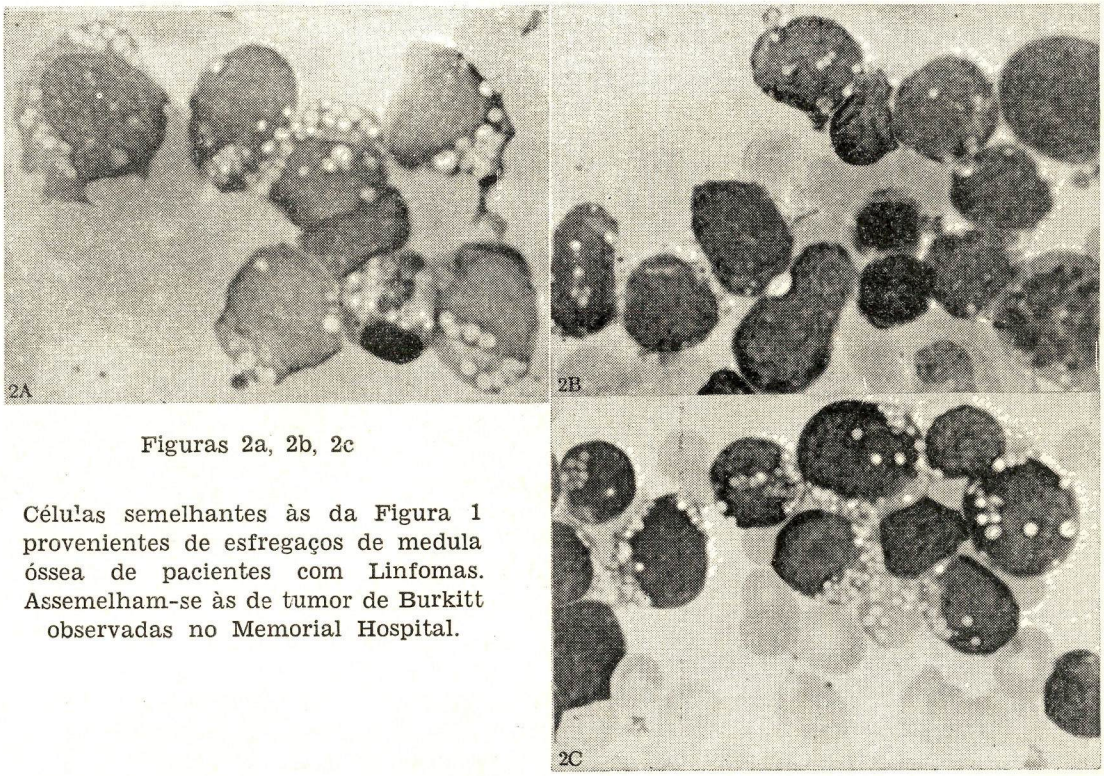


Figura 1a e 1b

Preparações de impressão coradas pelo May Grunwald - Giemsa e obtidas de pacientes com tumor de Burkitt em Kampala, pelo Dr. D. H. Wright.

de 60° F e chuvas que ultrapassem 20 polegadas por ano. No que concerne a vetores artrópodos a área endêmica corresponde, de maneira muito aproximada, à existência de mosquitos (85). Os tipos Anopheles e Mansonia são os que se ajustam melhor a esta distribuição. (4, 85).

No que concerne a virus, quer do ponto de vista etiológico, quer como agentes passageiros, uma partícula de virus semelhante ao do herpes foi encontrada por Epstein (19, 21), Stewart (79), O'Conor (57) e outros, em muitas linhagens de cultura de células, não apenas provenientes de Kampala, porém, em vários casos, por isolamentos diferentes, em Ibadan e nos Estados Unidos. A fig. 3-A mostra partículas de virus em uma célula da linhagem Jiyoye (68, 70), isolada por Osunkoya e Pulvertaft e examinada por De Harven (comunicação pessoal). Tais partículas também foram encontradas em doentes nativos dos Estados Unidos e em casos em que o isolamento foi feito nos Estados Unidos, porém, em paciente originário de Ibadan. Bell (5) também isolou virus Reo em vários casos de tumor de Burkitt, e, anticorpos para o Reo 3 foram encontrados em 73% dos pacientes de linfoma e em 18% dos casos de contrôle. Stanley (77) relatou ter evidenciado infecções pelo Reo 3 em mosquitos da Austrália, e que êstes virus produzem síndrome de nanismo em camundongos. O baço de alguns dêstes camundongos com



Figuras 2a, 2b, 2c

Células semelhantes às da Figura 1 provenientes de esfregaços de medula óssea de pacientes com Linfomas. Assemelham-se às de tumor de Burkitt observadas no Memorial Hospital.

nanismo também produzem nanismo e, ocasionalmente linfomas, em camundongos isólogos.

Burkitt (9), Ngu (55) e Clifford (14) relataram os resultados obtidos com a quimioterapia no tratamento desta doença. O Methotrexate foi eficaz quando administrado em regime de doses semelhante ao usado por Hertz (36) no coriocarcinoma, e produziu remissões prolongadas nos casos precoces, porém, foi menos eficiente nos casos moderadamente adiantados e nos muito avançados. (59). Não teve qualquer ação quando empregado na pequena dose

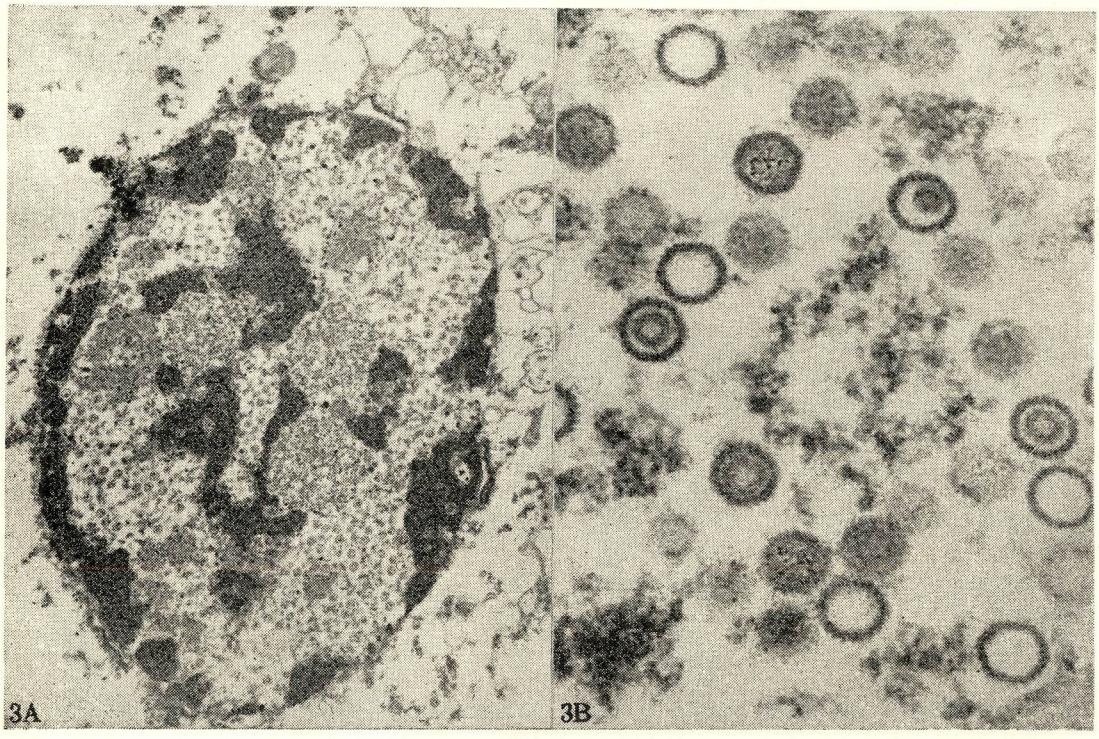


Figura 3a

Núcleo degenerado da linhagem de células "JIYOYE". O citoplasma já desapareceu quase completamente e a cromatina está marginalisada e condensada. Vêm se muitas partículas entre as massas de cromatina. Estas partículas têm diâmetros quase idênticos e sua estrutura fina é vista melhor na Fig. 2. Coloração para microscopia eletrônica com uranyl e chumbo. Aumento de 16.000 vêzes.

Figura 3b

Proveniente de outra amostra da linhagem "JIYOYE", envelhecida propositadamente para aumentar o número de células em degeneração. Êste maior aumento de microfotografia eletrônica mostra a estrutura fina das partículas freqüentemente observadas dentro dos núcleos das células em degeneração. Estas partículas têm, em média, 100 a 110 mu de diâmetro. Aparecem inicialmente nos núcleos das células em degeneração e adquirem uma membrana adicional em uma fase citoplásmatica subseqüente do seu desenvolvimento. Do ponto de vista morfológico assemelham-se muito aos vírus do grupo herpes. Preparação corada com uranyl e chumbo. Aumento de 94.000 vêzes.

diária, oral, que usualmente se administra aos doentes de leucemia aguda. A Ciclofosfamida (Enduxan, Cytoxan), parece ser tão eficaz quanto o methotrexate em casos iniciais e mais eficaz do que êle em casos moderada ou grandemente avançados (9, 60, 13). Outros agentes alquilantes, como o Melphalan e o Orthomelphalan, são também ativos (14). A vincristina produziu regressões rápidas, porém passageiras e, na maior parte dos casos, o tumor de localização extra-mandibular, recidivou ràpidamente. Isto parece ser comparável ao que sucede na leucemia aguda, na qual a vincristina provoca remissões com grande rapidez porém, se o tratamento é interrompido, a remissão é relativamente curta. Surpreendentemente, a vinblastina, a prednisona, a 6-mercaptopurina e a metilhidrazina parecem ser ineficazes nos casos estudados.

O aspecto importante do tratamento do tumor de Burkitt, e isto se relaciona particularmente ao methotrexate e ao Enduxam, é a ocorrência de longa sobrevivência, que algum dia poderá ser chamada de "cura". Se somarmos os 88 casos relatados por Burkitt (9), os 54 de Ngu (53, 55) e os 39 de Clifford (14), veremos que houve regressões completas em 40% dos casos de Burkitt, em 24% nos de Ngu e em 21% nos de Clifford. Dos 25 casos, ou 14%, que presentemente estão perfeitamente bem, sem qualquer sinal da doença e sem qualquer tratamento de manutenção, Burkitt tem 14, Ngu, cinco e Clifford, seis. Dêstes pacientes 3 já sobrevivem entre 6 meses e um ano, 6 pacientes entre 1 e 2 anos, seis entre 2 e 3 anos, sete entre 3 e 4 anos, e três entre 4 e 6 anos. Burkit (9) afirma nunca ter visto recidiva em paciente que tivesse permanecido em remissão durante 12 meses, após a interrupção do tratamento. A figura 4 mostra doze dêstes sobreviventes a longo prazo, como foram apresentados na Conferência de Kampala, por Burkitt, em janeiro de 1966.

Figura 4

Paciente com tumor de Burkitt sem sinais de doença por períodos de seis meses a seis anos depois da interrupção do tratamento.

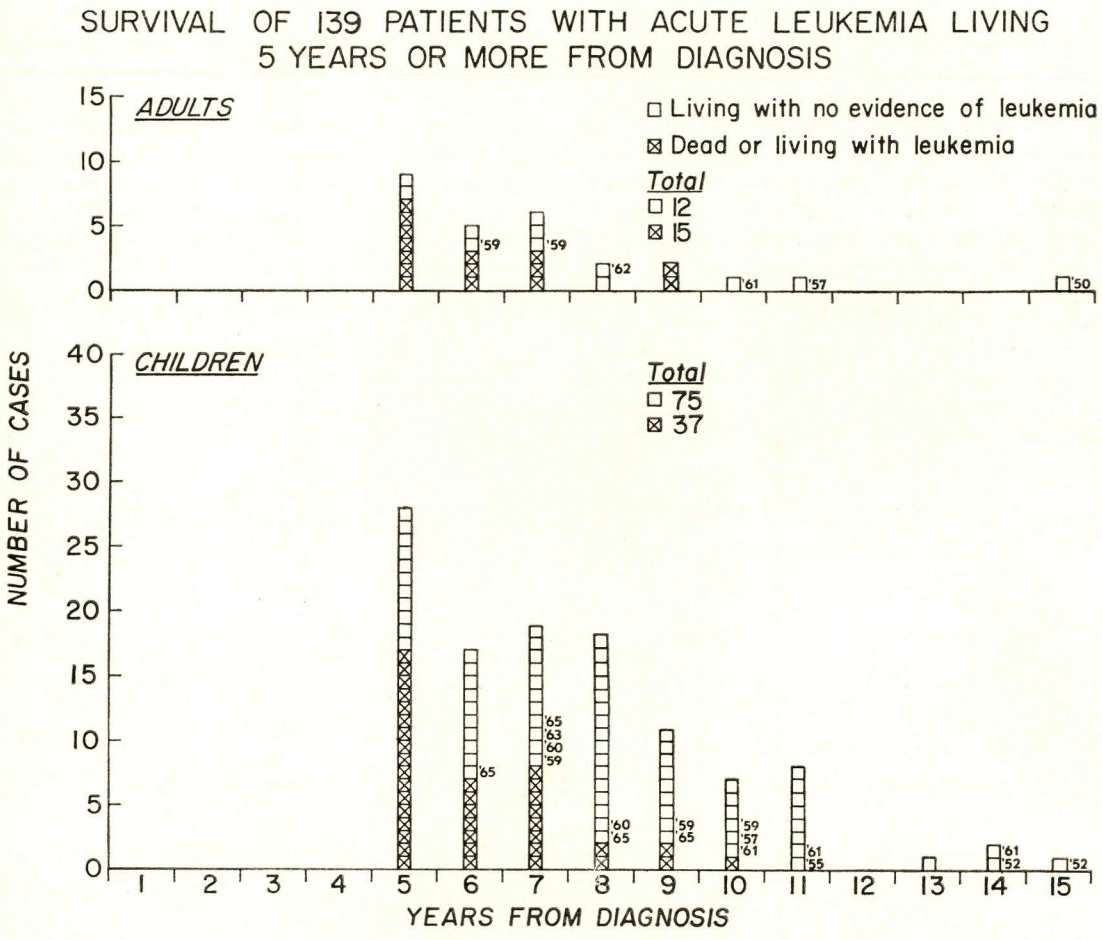


Figura 5

139 pacientes com leucemia aguda que sobreviveram mais de 5 anos a contar da data do diagnóstico, de uma pesquisa mundial levada a cabo sob o patrocínio da "Acute Leukemia Task Force". Os números após os quadrados abertos indicam o ano em que o tratamento terminou.

Um número significativo dêstes 181 casos não pôde ser seguido clìnicamente (follow-up), sendo que alguns dêles poderão aparecer posteriormente sendo então incluídos no grupo dos que não apresentavam sinais de doença. Se retirarmos o número correspondente a êstes pacientes que não foram seguidos, com o argumento de que é possível, senão muito provável, que o fato de não terem voltado ao hospital é devido a estarem curados, e não porque morreram, chega-se à conclusão de que Burkitt tem nos seus 40% de casos em remissão completa, 52% curados. Isto daria, aproximadamente, 20% do grupo inicial, sem sinal de doença. Esta cifra é muitíssimo mais alta do que a encontrada em qualquer outro tumor espontâneo, inclusive leucemia aguda. Nesta última doença, segundo o relatório do "Acute Leukemia Task Force Long Term Survivors Registry", figura 5, vê-se, presentemente, 139 pacientes que sobreviveram 5 anos ou mais após o diagnóstico de deucemia aguda. Doze de 27 adultos e 75 de 112 crianças estão vivos e bem, sem sinais de leucemia, 5 a 15 anos após o diagnóstico. O número total de pessoas componentes da população de leucêmicos que deu

êste número de sobreviventes é desconhecido e, desta forma, não se tem idéia do percentual de incidência dêstes sobreviventes após 5 e 15 anos. As maiores cifras, até a presente data, para sobreviventes de 5 anos, são as de Zuelser (88 — comunicação pessoal), que teve 10 sobreviventes com 5 anos, em 285 casos consecutivos de leucemia aguda em crianças que se internaram no Detroit's Children's Hospital, o que dá sobrevivência de 5 anos, em 3,5% dos casos. Naturalmente, no coriocarcinoma, cêrca de 75% dos casos têm sobrevida longa (35), presumìvelmente cura, porém, trata-se de tumor transplantado, de origem fetal e não um tumor espontâneo do hospedeiro.

Quanto à pesquisa de novos agentes quimioterápicos, Goldin (30) analisou técnicas de busca (enquadramento) que podem ser úteis no tumor de Burkitt. Parece que a leucemia L-1210 do camundongo e o carcinoma 256 de Walker, do rato, absorvem a maioria das substâncias que demonstraram ter atividade clínica, tais como o Enduxam, o Methotrexate, a Vincristina, a Actinomicina D, o Melphalan e o Orthomerphalan, da mesma forma que as células da leucemia aguda.

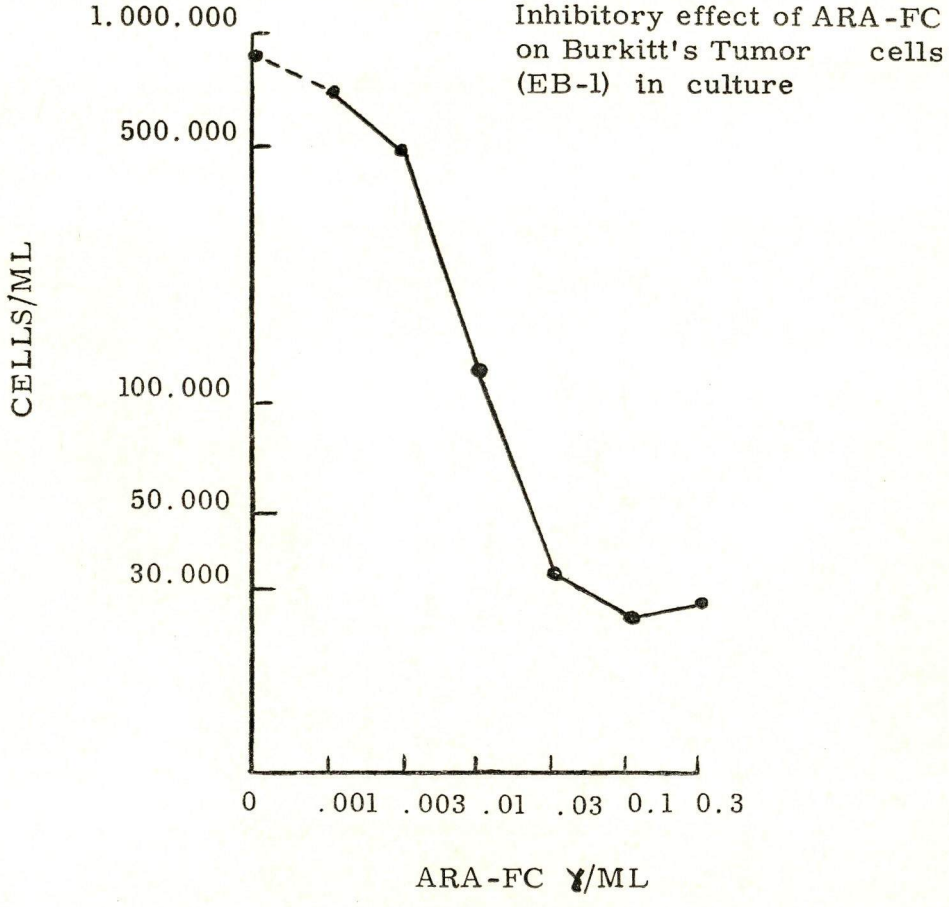


Figura 6

Efeito inibidor da ARA-FC sôbre as células do tumor de Burkitt (EB-1) em cultura.

O próprio tumor de Burkitt, também, pode ser adaptado ao estudo de enquadramento, utilizando técnicas **in vitro.** Foi demonstrado por Epstein (20, 23), Pulver-

taft (69) e Osunkoya (66, 67), que linhagens contínuas de células de tumor de Burkitt podem ser obtidas em culturas de células, com grau considerável de regularidade. A dose inibitória de 50% (ID.50), de vários compostos contra estas linhagens pode ser determinada com relativa facilidade. Osunkoya e nosso grupo (66,8) já referiram que as culturas de células, usando várias linhagens de células de tumor de Burkitt, podem ser úteis na avaliação de novos agentes em potencial, porém, ainda é muito cedo para tentar fazer qualquer correlação clínica.

Usamos em nossos estudos uma modificação da técnica de Fischer (25). Linhagens celulares do tumor de Burkitt EB-1, 2 e 3, isoladas por Epstein (20, 23), e as raças Kudi e Ogun, isoladas por Pulvertaft e Osunkoya (67, 69), foram semeadas em meio de Ealge, chamado de "meio mínimo essencial" (MEM), ao qual se juntou. aminoácidos não essenciais, extra glutamina, 15% de sôro de feto de vitela, 200 un/ml de penicilina e 200 mcg/ml de esptreptomicina. Usamos inicialmente uma concentração celular de 30.000/ml e as células foram colocadas em 5 ml do meio, em tubos de 16 ml com tampa de aparafusar pela técnica de Fischer. Os tubos foram fortemente arrolhados e incubados por 168 horas a 37° C. As contagens de contrôle ao fim dêste tempo oscilavam, usualmente, entre 250.000 células (3 gerações) e 1 milhão de células/ /ml (5 gerações).

A figura 6 mostra o efeito de concentrações variadas de 1-A-D-arabino-furanosy-5-fluorocytosina no crescimento de crescimento de células de Burkitt da linhagem EB-1. A Tabela I mostra a ID 50 para a EB-1 de um número de antimetabólicos, agentes alquilantes, antibióticos e substâncias derivadas de fontes naturais. Pode-se ver que dos vários anti-metabólicos 1-B-D-arabino-furanosyl-cytosina (ara C) e a 1-B-D-arabino-furanosyl-5-fluorocytosina (ara-FC), com uma ID-50 de, aproximadamente 0,003 a 0,005 un/ml parecem ser iguais ao methotrexate, porém, considerà-

TABELA 1

DOSE INIBIDORA DE 50% CONTRA A LINHAGEM EB-1 DE CÉLULAS DE TUMOR DE BURKITT EM CULTURA

COMPOSTO	DOSE (γ/)
ARA-FC	0.003
ARA-C	0.005
METHOTREXATE	0.008
6-MERCAPTOPURINA	3.0
HYDROCORTISONA	40.0
ACTINOMICINA D	0.002
VINCRISTINA	0.005
DAUNOMICINA	0.08

velmente melhores do que a 6-mercaptopurina com uma ID-50 de, aproximadamente, 3 ug/ml. A mostarda nitrogenada e o thio-Tepa foram moderadamente ativas, tendo como ID-50, aproximadamente, 0,2 ug/ml. A ciclofosfamida (Cytoxan, Enduxan) por outro lado, embora muito ativa clìnicamente, foi ineficaz neste sistema, como era de esperar, uma vez que há necessidade de ativação da droga no fígado, para que exerça efeito citotóxico. A vincristina e a Actinomicina D foram muito ativas, com uma ID-50 de 0,005 ug/ml e 0,001 ug/ml respectivamente.

A ID-50 da vincristina, methotrexate, e ara-FC, contra um espectro de 6 linhagens

de cultura de células de tumor de Burkitt, estão representadas na Tabela 2. Há, no máximo, uma variação de 3 vêzes na sensibilidade. O emprêgo dêste sistema para estudar os mecanismos de ação está demonstrado pelo bloqueio do efeito inibidor da ara-FC pela deoxycytidina (Fig. 7). Outros estudos mostraram que esta inibição não pode ser bloqueada pela cytidina, thymidina, adenosina.

A maior desvantagem de técnica de busca que utilize culturas de tecido é a falta de contrôle da toxicidade inespecífica das substâncias. Nestes estudos procuramos evitar êste impecilho comparando a ID-50 nas células de tumor de Burkitt e nas da leucemia P-815 do camundongo reproduzidas **in vitro**, com dose máxima tolerada no homem (MTD), e a dose mínima diária eficaz (MED) no camundongo. Desta forma, para determinado composto, a MTD (em mg/kg) do homem dividida pela MED (em mg/kg) do camundongo é igual ou maior do que a ID-50 (em ug/ml) para as células do tumor de Burkitt, dividida pela ID-50 (em ug/ml) para as células de leucemia do camundongo, a substância deve ser eficaz contra o tumor de Burkitt, no paciente, partindo do pressuposto de que não haja diferenças qualitativas ou quantitativas no metabolismo do composto.

$$\frac{\dfrac{\text{MDT homem}}{\text{MED camundongo}}}{\dfrac{\text{ID-50 células de Burkitt}}{\text{ID-50 células de camundongo}}} =$$

Desta forma a dose de 1,0 mg/kg por dia, em pacientes, durante 5 a 8 dias, produziu regressão completa em uma alta percentagem de tumores iniciais e, no camundongo, 1,0 mg/kg, por dia, durante 5 a 10 dias, foi também uma dose eficaz. É ativa, na cultura de células, contra EB-1, na concentração de 0.008 ug/ml e semelhantemente ativa contra as células da leucemia P-815-Y do camundongo. Cálculos semelhantes com a ara-C mostram um índice ainda mais favorável (8).

Há necessidade de aguardar maior correlação clínica para saber se essa técnica será útil para a seleção de novos agentes, clìnicamente ativos, em relação ao tumor de Burkitt; os estudos prelmiinares porém, sugerem que êste possa ser realmente um teste simples e prático.

TABELA 2

DOSE INIBIDORA DE 50% CONTRA LINHAGENS DE CULTURAS DE CÉLULAS OBTIDAS COM CÉLULAS DO TUMOR DE BURKITT

LINHAGENS DE CULTURAS DE CÉLULAS	DOSE (ɣ / ML)		
	VCR	MTX	ARA-FC
EB-3	0.005	0.008	0.003
EB-1	0 005	0.02	0.01
EB-2	0.005	0.02	0.003
SL - 1	0.005	0.03	—
KUDI	0.002	0.008	0.01
OGUN	0.005	0.02	0.01

Os estudos pormenorizados de Skipper e seu grupo (75, 76), sôbre o conceito de destruição total das células neoplásicas, parecem particularmente pertinentes no tumor de Burkitt, de vez que a morte do total de células parece ter sido conseguida, ocasionalmente, nesta doença. Isto, ao que tudo indica foi obtido ùnicamente pela quimioterapia e, como era de esperar, em tumor muitos investigadores são de opinião que, à luz da presente ineficiência da quimioterapia do câncer em geral, qualquer sobrevivente a prazo longo, em qualquer doença tratada pela quimioterapia, constitui prova a favor da existência da "defesa do hospedeiro". Cada um daqueles autores relatou um caso com remissão temporária que durou de 2 a 3 semanas, após a administração

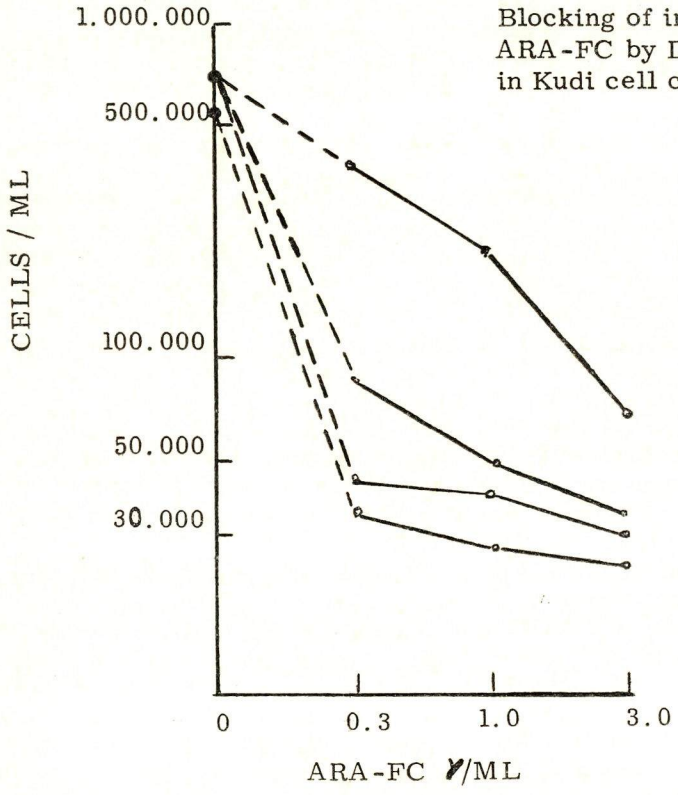


Figura 7

Bloqueio da ação inibidora da ARA-FC pela Deoxycytidina (CdR) na cultura de células de Kudi (168 horas).

sensível. Todavia, o mais provável é que êsses resultados sejam devidos à soma dos fatôres: sensibilidade ao quimioterápico e resistência do hospedeiro.

Burkitt (10) e Ngu (54) apresentaram provas clínicas de que há defesa do hospedeiro. Descreveram regressões, algumas espontâneas, e algumas, ao que parece, após terapêutica inadequada. Na realidade, venosa de 100 a 150 ml de plasma de pacientes com tumor de Burkitt em completa remissão. Klein et al. (42) demonstraram que o sôro de pacientes em remissão completa reagia positivamente à reação indireta de membrana imunofluorescente, contra um espectro de células-alvo, vivas, de Burkitt, em maior proporção do que o sôro de pacientes em remissão parcial ou que não ex-

perimentaram remissão. Os sôros de pacientes com leucemia aguda, na Suécia, reagiram negativamente frente às mesmas células. Os parentes sadios dos pacientes com tumor de Burkitt reagiam, usualmente, de forma negativa. Klein (42) declara que, embora a especificidade não possa ser tida como estabelecida de maneira conclusiva, pode ser sugerida pelos seguintes fatos: 1) freqüência semelhante de reações positivas obtidas com células-alvo de Burkitt autóctones e alogênicas em 5 dos 6 casos nos quais foi possível fazer tal comparação; 2) tendência dos sôros positivos para reagirem com tôdas ou com a maior parte das células-alvo de Burkitt testadas, obtidas de 5 a 9 pacientes diferentes, na maioria dos casos; 3) ausência de reação contra outras células alogênicas que não eram células-alvos de Burkitt; 4) ausência de qualquer relação entre a aglutinação de hemácias, imunofluorescência, e fluorescência de células-alvo de Burkitt nos casos em que ambas derivavam do mesmo doador; 5) ausência de reatividade contra células normais da medula óssea das células-alvo de Burkitt do doador, quando testadas contra os mesmos sôros Burkitt-positivos.

Os Henles (1, 33, 34) estudaram linhagens de células cultivadas do tumor de Burkitt pelas técnicas de imunofluorescência e fixação do complemento. Pela primeira, todos os 17 sôros de pacientes com tumor de Burkitt foram positivos, em comparação com 35% de positividade encontrada para o sôro de crianças americanas com leucemia, tumores sólidos ou outras doenças. Oitenta e cinco por cento do sôro de adultos normais, entretanto, reagiu positivamente. Pela técnica de fixação do complemento, 12 em 13 sôros, em casos de tumor de Burkitt, foram positivos, contrastando com 20% dos sôros de crianças americanas e 60% dos adultos. As reações de imunofluorescência parecem diferir das relatadas por Klein et al. no fato de que a reação de Henle depende, provàvelmente, da presença de um virus semelhante ao de herpes, nas linhagens estabelecidas, enquanto a reação de Klein parece medir um antígeno da membrana celular presente na superfície de células recém-biopsiadas, mas não presente, pelo menos em concentração elevada, nas linhagens celulares estabelecidas (Klein, 6, comunicação pessoal).

Osunkoya (68) relata a existência de fatôres de inibição em muitos sôros normais contra células recém-isoladas do tumor de Burkitt, enquanto que o sôro de pacientes com tumor de Burkitt não teve o efeito inibidor. Desde que o tumor de Burkitt começasse a crescer em cultura contínua, êstes sôros normais pareciam ter efeito de estímulo de crescimento, que o sôro de doentes com tumor de Burkitt não tinha.

Êstes vários caminhos de pesquisa sugerem que o tumor de Burkitt tem grandes implicações com a leucemia aguda. Mesmo com o reduzido número de medicamentos disponíveis na África, 15 a 20% dos tumores de Burkitt podem ser tratados e desaparecer por longos períodos. Há boa possibilidade de que, com o acréscimo de alguns dos novos agentes, presentemente disponíveis, e terapêutica combinada intensiva, o nível de bons resultados se eleve a 50%. Porque o tratamento do tumor de Burkitt é mais eficaz e duradouro na África, do que o tratamento da leucemia aguda na Europa e nos Estados Unidos? O tumor de Burkitt nos Estados Unidos responde de maneira diferente do africano? O que pode ser aprendido com o tumor de Burkitt que possa ajudar no contrôle da leucemia? Estas perguntas sugerem especulação de longo alcance.

Examinemos por um momento a possibilidade de que o tumor de Burkitt esteja, de alguma forma, relacionado a leucemia aguda, como Dalldorf (15) e outros sugeriram, talvez sendo mesmo causado pelo mesmo estímulo, que é limitado pela imunidade a tumores localizados, talvez relacionado a tipos e tempos diferentes de exposição ao estímulo hipotético, ou talvez estimulado de maneira inespecífica por infecções bacterianas ou infestações parasitárias. Se o caso fôsse êste, o paciente já deveria ter alguma resistência de hospedeiro. Há analogias nas leucemias de roedores. Uma inoculação sub-cutânea de células leucêmicas que induza leucemia generalizada e ràpidamente fatal em um camundongo, com alguma defesa de hospedeiro, na base de uma histo-incompatibilidade menor, produz um tumor sólido de crescimento lento. Uma situação possìvelmente análoga também ocorre na leucemia aguda. Entre os 139 sobreviventes de longo termo de leucemia aguda foram relatados

linfosarcomas de ovário ou de testículo, como primeiro sintoma de recorrência em oito pacientes.

Isto pode ser semelhante, de alguma forma, à situação existente no tumor de Burkitt. Havia, provàvelmente, alguma resistência do hospedeiro, comprovada pela sobrevivência por longo prazo depois da quimioterapia, porém um tumor localizado desenvolveu-se eventualmente. O fato de que alguns dêstes tumores puderam ser tratados por terapêutica localizada, e nunca ocasionaram leucemia generalizada, reforça a prova da existência de resistência do hospedeiro. Talvez as células neoplásicas, em presença de um certo grau de resistência do hospedeiro, como devia haver nos sobreviventes de prazo longo de leucemia aguda, e nos pacientes com tumor de Burkitt, possam apenas dar origem a um nódulo localizado, em uma comunidade onde possam obter algum apoio mútuo e proteção contra um ambiente hostil. Klein (41) estabeleceu o postulado de que, se a leucemia e o tumor de Burkitt forem causados pelo mesmo agente, pode haver transmissão vertical da mãe para o feto dentro do útero, na leucemia, e neste caso pode-se esperar que haja completa tolerância imunológica. Por outro lado, se o agente, no tumor de Burkitt, fôr transmitido por um vetor artrópode algum tempo depois do nascimento, seria razoável a existência de um certo grau de resistência do hospedeiro, por analogia com as inoculações com o virus SV-40 e do polyoma no recém-nato, versus no adulto.

Quanto às possíveis alterações do sistema retículo-endotelial, temos que levar em conta que são comuns as infecções repetidas nas populações em que se encontra o tumor de Burkitt. Old et al. (64) demonstraram que o grau de depuração do carbono coloidal do sangue é muito aumentado em camundongos prèviamente inoculados com BCG. As infecções com BCG tornam os camundongos mais resistentes às infecções por virus e também a doses letais mínimas de radiação ionizante (2, 61, 63, 65). Êste tratamento também produziu um aumento da respostas imunitária a vários antígenos. Biozzi et al. (7) e Hapern et al. (31) mostraram que há inibição do crescimento da ascite de Ehrlich em camundongos e do carcinoma uterino de Guerin em ratos prèviamente infectados com BCG. Os efeitos protetores também foram demonstrados por Old et al. (61, 62, 65) no sarcoma 180, na ascite de Ehrlich e no carcinoma 755. Lemonde (45, 46) demonstrou que o BCG exerce efeito inibidor sôbre o crescimento da leucemia transplantada e reduz a incidência de alterações malignas, prolongando a sobrevida de "hamsters" inoculados com BCG, seguido do virus polyoma uma semana após o nascimento. Weiss et al. (84) mostraram que frações do bacilo da tuberculose (MER) têm atividade protetora contra tumores isólogos em camundongos. Steinkuller et al. (78) ampliaram ainda mais êstes estudos sôbre o MER. Weiss et al. (84) assinalam que, se a doença neoplásica progressiva é em realidade uma manifestação de deficiência imunológica, seria de esperar que as substâncias que aumentam a produção de anticorpos e a eficiência das reações que libertam o organismo de substâncias extranhas, aumentassem também a resistência ao desenvolvimento dos tumores malignos. Tivemos em mente estas esperanças na realização dos vários sistemas experimentais de tumores mencionados acima e, parece, dentro dos limites da possibildiade, que as muitas e repetidas infecções que essas crianças sofreram aumentou a capacidade do hospedeiro para desenvolver imunidade específica ao tumor de Burkitt.

Além disto, a maior parte dos pacientes com tumor de Burkitt, provém de zonas da África onde a malária é hiper-endêmica e a maior parte dos pacientes mostrava sinais de infestação malárica prévia (aumento do baço, pigmento malárico, etc). Esta hipertrofia do sistema retículo-endotelial poderia também aumentar a capacidade do hospedeiro para reagir a um estímulo específico (29). Barnett (3) mostrou que da infecção concorrente de canários com o parasito de malária, Plasmodium relictum, e o virus da encefalite eqüina do oeste, resultava em significativa supressão do título de virus nessas aves. Trager (81, 82) demonstrou que suspensões de Tumor de Galinhas, injetadas em pintos com 2 a 3 semanas de idade, cresciam mais vagarosamente, e ocasionalmente nem cresciam, se fôssem feitas injeções de Plasmodium lophurae no mesmo dia ou no dia seguinte. Assim que os pintos se curavam da infecção malárica, entretanto, o tumor crescia com a mesma rapidez que nos contrôles.

Nadel et al. (52) usando Plasmodium berghei e leucemia L-1210 observaram aumento no tempo de sobrevida se a malária era inoculada antes.

Para reproduzir a mesma situação que ocorre no tumor de Burkitt seria provàvelmente necessário inocular repetidamente camundongos com malária até que algum grau de imunidade à malária se instalasse. Isto é difícil de conseguir com uma raça agudamente virulenta como o P. berghei, que mata em 7 a 10 dias, embora seja possível que inoculações repetidas, com a infecção terminada, ou pelo menos efetivamente suprimida no 5º ou 6º dia, com cloroquina, pudesse eventualmente produzir o grau desejado de estímulo retículo-endotelial. O tipo de infecção mais crônica pelo Plasmodium chabaudi (43, 44), seria provàvelmente mais eficaz. Êstes camundongos devem então ser inoculados com doses gradativas e o efeito da leucemia e da terapêutica antileucêmica comparados nestes camundongos e camundongos sem malária. Tais estudos estão agora em andamento em nosso laboratório.

Nos últimos 60 anos tem havido vários relatos clínicos dos efeitos benéficos temporários da malária na leucemia (51, 71, 73) e doenças afins (40), porém êstes exemplos têm sido, principalmente, em leucemias crônicas, com recaídas floridas e, em nenhum dêles, o paciente estava em remissão completa quando a malária foi inoculada. Diminuições temporárias nas contagens totais de leucócitos foram observadas, mas não houve nenhuma influência favorável de caráter permanente (72, 73, 28).

Em um caso de leucemia aguda, entretanto, em um rapaz de 14 anos, tratado provocando infecção com o Plamodium vivax, relatado por Lucherini (49), a contagem de leucócitos caiu de 250.00, com 73% de mieloblastos, para 4.400, depois de 12 episódios febris em 16 dias e, depois de decorridas 6 semanas da febre ter sido tratada com quinino, os leucócitos ainda eram 5.800, com uma contagem diferencial normal e hematimetria de 4.4 milhões/mlc. Houve um decréscimo na esplenomegalia e nas linfadenopatias e notável melhora do estado geral. Infelizmente não foi registrada a seqüência posterior do seguimento.

Todos êstes estudos sugerem que infecções maláricas prévias em crianças com tumor de Burkitt podem, em verdade, ter influência na resposta ao tumor.

O que pode ser aprendido com o tumor de Burkitt que venha a ser de utilidade no tratamento da leucemia? A quimioterapia dêste tumor difere consideràvelmente, no esquema de doses, do esquema empregado em leucemias agudas. O Methotrexate em doses diárias, dadas por via oral não tem efeito no tumor de Burkitt, como ficou demonstrado por Oetgen et al. (59), porém tratamentos maciços a curto prazo são eficazes. Isto é particularmente interessante em vista dos trabalhos de Li, Hertz et al. (47, 48) de que doses maciças durante 5 dias foram mais eficazes no coriocarcinoma do que pequenas doses diárias de methotrexate, dadas até atingir o mesmo grau de toxicidade, e também dos trabalhos de Selawry et al. (74), no qual doses maciças intramusculares de methotrexate, duas vêzes por semana, foram superiores a doses orais diárias para manutenção de remissão em crianças com leucemia aguda. O Enduxan também tem sido muito mais eficaz no tumor de Burkitt quando administrado em doses únicas, macicas, repetidas cada 2 ou 3 semanas (9). Talvez se devesse refletir mais sôbre êsses fatos no que se refere à leucemia aguda. A dificuldade, nos estágios iniciais das leucemias agudas, é que a medula óssea tem quantidades insuficientes de precurssores de leucócitos, hemácias e plaquetas pelo que há perigo de agravar o deficit com terapêutica macica. Alguns estudos neste sentido estão sendo feitos, conforme publicações do National Cancer Institute e do Grupo B de Leucemia (26, 27, 32, 37, 39), porém, é preciso que se faça ainda mais. Por exemplo, após a indução de remissão com vincristina e prednisona, deve-se seguir exatamente a técnica de tratamento preconizada por Burkitt com o Enduxan: 2 doses venosas de 30 a 40 mg/kg, separadas por um intervalo de 2 a 3 semanas, e depois, nenhum outro tratamento até a recidiva. É importante executar exatamente a técnica porque Burkitt pode ter acertado e estabelecido a dose absolutamente correta. É possível que se houvesse êle administrado doses maiores ou menores, não tivesse obtido resultados tão satisfatórios.

O que pode ser fetio para anular o deficit imunológico e estimular as defesas do hospedeiro na leucemia aguda? Tomando

por base os debates da Conferência de Kampala e de outros locais, parecem promissoras certas medidas que visam a aumentar as defesas do hospedeiro. Algumas destas medidas já estão sendo estudadas, independentemente das sugestões provenientes do comportamento o tumor de Burkitt. Tôdas essas tentativas de imunização devem ser tomadas na ocasião em que o paciente com leucemia aguda está em remissão completa, de modo que o excesso antigênico seja reduzido ao mínimo. Não deve haver também tratamento de manutenção que interfira com a indução de imunidade ativa.

I. **Imunização Ativa**

A. Específica

(1) — **Infecção com células leucêmicas autólogas.** Devem ser colhidas quando o doente é admitido inicialmente no hospital, antes do tratamento, e multiplicadas em cultura celular e, se possível, guardadas em congelação até a data da utilização. Podem ser irradiadas e administradas sem alteração, ou homogeneisadas e irradiadas, ou tratadas pela técnica de Weigle (83), na esperança de vencer a tolerância.

(2) — **Infecção com células de tumor de Burkitt irradiadas.** Isto pode ser feito baseando-se na teoria de que o tumor de Burkitt pode ser um pouco mais antigênico do que a leucemia aguda e de que pode haver relação antigênica cruzada (24).

B. Procedimentos para aumentar a capacidade do hospedeiro de desenvolver imunidade específica.

(1) — **Vacinação com BCG ou fração MER.** Isto parece justificável em razão dos dados de experimentação apresentados acima.

(2) — **Indução de malária.** Por analogia com a documentação mencionada acima, poder-se-ia estabelecer o postulado de que a hipertrofia do sistema retículo-endotelial produzida pela malária pode aumentar a capacidade do hospedeiro para desenvolver imunidade específica, quer ao tumor e Burkitt, quer à leucemia, particularmente se a indução fôr feita na ocasião em que a leucemia estiver em completa remissão.

II. **Imunização Passiva**

Voluntários poderiam ser imunizados por infecções de células irradiadas, de pacientes com leucemia aguda ou tumor de Burkitt e, depois de algum tempo de circulação, ou após a demonstração da existência de anticorpos ligados às células, os pacientes com leucemia seriam transfundidos repetidamente com plasma obtido por plasmaforese, ou concentrados de leucócitos, ou fator de transferência de leucócitos, obtido por leucoforese, ou por canulisação do canal toráxico dos voluntários imunizados. Já mencionamos que Ngu e Burkitt produziram regressões temporárias, objetivas, com duração de 2 a 3 semanas, em pacientes que não tinham recebido qualquer forma de tratamento, portadores de doença ativa, depois da injeção venosa de plasma de outro paciente com tumor de Burkitt, em fase de remissão. Tal imunização passiva, particularmente se tentada na ocasião em que o paciente estiver em remissão produzida pela quimioterapia, parece ser merecedora de maiores estudos. O emprêgo de plasma e leucócitos provenientes de sobreviventes a longo têrmo parece particularmente pertinente.

Em resumo, o conhecimento atual do tumor de Burkitt sugere 3 maneiras de abordar o tratamento das leucemias agudas:

(1) — Depois que se produz remissão completa com vincristina e prednisona, administrar doses únicas, grandes, ou cursos de pequena duração, porém intensivos, de quimioterapia, que deve ser repetida a intervalos de 2 a 3 semanas.

(2) — Estudo cuidadoso dos pacientes em remissão completa e sem qualquer tratamento de manutenção para evidenciar as defesas do hospedeiro.

(3) — Tentativas de aumentar as defesas do hospedeiro por imunização ativa, específica ou não, ou por imunização passiva específica, na ocasião em que o paciente estiver em fase de remissão completa, porém, não mantida.

As remissões a longo prazo observadas no tumor de Burkitt são provàvelmente resultantes da ação combinada da quimioterapia e das defesas do hospedeiro, e esta visão bilateral do problema parece ser essencial na leucemia aguda.

O estudo da quimioterapia geográfica no tumor de Burkitt, comparando-se os resultados do tratamento e as provas de defesa do hospedeiro no paciente em remissão. na África, com documentação semelhante nos Estados Unidos, deverá resultar em valiosos elementos de orientação para o contrôle da leucemia.

BIBLIOGRAFIA

1 — ARMSTRONG, D. HENLE, G., and HENLE, W. — Complement-fixation tests with cell lines derived from Burkitt's lymphoma and acute leukemia. J. Bact., *91*:1257-62, 1966.

2 — BALNER, H., OLD, L. J., and CLARKE, D. A. — Reduction of x-ray lethality in mice by agents affecting the reticulo-endothelial system. Rad. Res., *15*:836-40, 1961.

3 — BARNETT, H. C. — Experimental studies of concurrent infection of canaries and of the mosquito *Culex Tarsalis* and *Plasmodium relictum* and Western equine encephalitis virus. Amer. J. Trop. Med. Hyg., *5*:99-109, 1956.

4 — BARNLEY, G. R. — Discussion of Williams' paper, "Implications of geographic distribution" in Session on "Epidemiology and Etiology in Relation to Chemotherapy", Conference on the Chemotherapy of Burkitt's Tumor, (Kampala, January 1966) Uganda.

5 — BELL, T. M. — Review of the evidence for a viral a etiology for Burkitt's lymphoma. *IN*: J. H. Burchenal and D. Burkitt (eds.), Treatment of Burkitt's Tumor, Berlin, Heidelberg, New York. Springer-Verlag, 1966, In press.

6 — BELTRAN, G., BAEZ, A. and CORREA, P. — Burkitt's lymphoma in Colombia. Amer. J. Med., *40*:211-16, 1966.

7 — BIOZZI, G., STIFFEL, C., HALPERN, B. N., and MOUTON, D. — Effet de l'inoculation du bacille de Calmette-Guérin sur le développement de la tumeur ascitique d'Ehrlich chez la souris. Compt. Rend. Soc. Biol., *153*:987-89, 1959.

8 — BURCHENAL, J. H., WIGGINS, R. M., and GUTHRIE, E. D. — Cell culture as a technique for evaluating potential chemotherapeutic agents for Burkitt's tumor. *IN*: J. H. Burchenal, and D. Burkitt, (eds.), Treatment of Burkitt's Tumor, *Op. Cit.*

9 — BURKITT, D. — Chemotherapy of jaw tumors. *Ibid.*

10 — ———— . — Clinical evidence euggesting the development of an immunological response against African lymphoma. *Ibid.*

11 — ———— . — A sarcoma involving the jaws in African children. Brit. J. Surg., *46*:216-23, 1958.

12 — ———— . — Some clinical features. *IN*: J. H. Burchenal and D. Burkitt, (eds.), *Op. Cit.*, In press.

13 — BURKITT, D., HUTT, M. S. R. and WRIGHT, D. H. — The African lymphoma: Preliminary observations on response to therapy. Cancer, *18*:399-410, 1965.

14 — CLIFFORD, P. — Observations on the treatment of Burkitt's lymphoma. *IN*: J. H. Burchenal, and D. Burkitt, (eds.), Treatment of Burkitt's Tumor, *Op. cit.* in press.

15 — DALLDORF, G. — Lymphomas of African children J.A.M.A., *181*:1026-28, 1962.

16 — DAVIES, A. G. H. and DAVIES, J. N. P. — Tumours of the jaw in Uganda Africans. Acta, U.I.C.C., *16*:1320, 1960.

17 — DORFMAN, R. F. — Childhood lymphosarcoma in St. Louis, Missouri, clinically and histologically resembling Burkitt's tumor. Cancer, *18*:418-30, 1965.

18 — EDINGTON, G. M., and MACLEAN, C. M. U. — Incidence of the Burkitt tumour in Ibadan, West Nigeria. Brit. Med. J., *1*:264-66, 1964.

19 — EPSTEIN, M. A., ACHONG, B. G., and BARR, Y. M. — Virus particles in cultured lymphoblasts from Burkitt's lymphoma. Lancet, *2*:702-03, 1964.

20 — EPSTEIN, M. A., and BARR, Y. M. — Characteristics and mode of growth of a tissue culture strain (EB_1) of human lymphoblasts from Burkitt's lymphoma. J. Natl. Cancer Inst., *34*: 231-40, 1965.

21 — ———— . — Cultivation *in vitro* of human lymphoblasts from Burkitt's malignant lymphoma. Lancet, *1*:252-53, 1964.

22 — EPSTEIN, M. A., BARR, Y. M., and ACHONG, B. G. — The behaviour and morphology of a second tissue culture strain (EB_2) of lymphoblasts from Burkitt's lymphoma, Brit. J. Cancer, *19*:108-15, 1965.

23 — ————. — Studies with Burkitt's lymphoma. Wistar Inst. Symposium Monographs, *4*:69-79, 1965.

24 — FINK, M. A., MALMGREN, R. A., RAUSCHER, F. J., ORR, H. C., and KARON, M. — Application of Immunofluorescence to the study of human leukemia. J. Natl. Cancer Inst., *33*: 581-83, 1964.

25 — FISCHER, G. A. — Studies of the culture of leukemia cells *in vitro*. Ann. N. Y. Acad. Sci., *76*:673-80, 1958.

26 — FREIREICH, E. J., KARON, M., FLATOW, F., and FREI, III, E. — Effect of Intensive cyclic chemotherapy (BIKE) on remission duration in acute lymphocytic leukemia. Proc. Am. Assoc. Cancer Res., *6*:20, 1965.

27 — FREIREICH, E. J., KARON, M., and FREI, III, E. — Quadruple combination therapy (VAMP) for acute lymphocytic leukemia of childhood. *Ibid*, 5: 1964.

28 — GAMBLE, C. J. — Failure of therapeutic malaria in treatment of leukemia. J.A.M.A., *88*:87-90, 1927.

29 — GOBLE, F. C., and SINGER, I. — The reticuloendothelial system in experimental malaria and trypanosomiasis. Ann. N. Y. Acad. Sci., *88*:149-171, 1960.

30 — GOLDIN, A. — Potential techniques for developing new chemotherapeutic agents for use in Burkitt's tumor. *IN*: J. H. Burchenal, and D. Burkitt, (eds.), *Op. Cit.*, in press.

31 — HALPERN, B. N., BIOZZI, G., STIFFEL, D., and MOUTON, D. — Effet de la stimulation du système réticuloendothelial par l'inoculation du bacille de Calmette-Guerin sur le développement d'épithelioma atypique t-8 de Guérin chez le rat. Compt. Rend. Soc. Biol., *153*:919-23, 1959.

32 — HENDERSON, E. S., FREIREICH, E. J., KARON, M., and ROSSE, W. — High dose combination chemotherapy in acute lymphocytic leukemia of childhood. Proc. Am. Assoc. Cancer Res., 7:30, 1966.

33 — HENLE, G., and HENLE, W. — Evidence for a persistant viral infection in a cell line derived from Burkitt's lymphoma. J. Bacteriol., *89*:252-58, 1965.

34 — ————. — Immunofluorescence in cells derived from Burkitt's lymphoma. *Ibid*, *91*:1248-56, 1966.

35 — HERTZ, R. — Eight years experience with the chemotherapy of choriocarcinoma and related trophoblastic tumors in women. Proc. UICC Conference on the Chemotherapy of Choriocarcinoma, (Baguio 1965), Philippines.

36 — HERTZ, R., LEWIS, Jr., J., and LIPSETT, M. B. — Five years experience with the chemotherapy of metastatic choriocarcinoma and related trophoblastic tumors in women. Amer. J. Obst. and Gyn., *82*:631-40, 1961.

37 — HOLLAND, J. F. — Intensive high dose treatment of children in complete remission of acute lymphocytic leukemia. *IN*: J. H. Burchenal and D. Burkitt, (eds.), Treatment of Burkitt's Tumor, *Op. cit.*

38 — HUTT, M. S. R. — The pathology of Burkitt's tumour in the context of lymphomas and leukemias. *Ibid.*

39 — KARON, M., FREIREICH, E. J. and CARBONE, P. — Effective combination therapy of adult leukemia. Proc. Am. Assoc. Cancer Res., *6*34, 1965.

40 — KLAUDER, J. V. — Fever therapy of mycosis fungoides. J.A.M.A., *106*:201-06, 1936.

41 — KLEIN, G. — Chairman of Discussion of "Host Defenses in Relation to Chemotherapy", Conference on the Chemotherapy of Burkitt's Tumor, (Kampala, January 1966), Uganda.

42 — KLEIN, G., CLIFFORD, P., KLEIN, E., and STJERNSWÄRD, J. — Search for tumour specific immune reactions in Burkitt's lymphoma patients by the membrane immunofluorescence reaction. *IN*: J. H. Burchenal, and D. Burkitt, (eds.), Treatment of Burkitt's Tumor, *Op. cit.*

43 — LANDAU, I., and CHABAUD, A. G. — Infection naturelle par deux *plas-*

modium du rongeur Thamnomys rutilans en Republique Centre Africaine. C. R. Acad. Sci. Paris, *261*:230-32, 1965.

44 — LANDAU, I. — Déscription de Plasmodium chabaudi n. sp., parasite de Rongeurs africains. C. R. Acad. Sci. Paris, *260*: 3758-61, 1965.

45 — LEMONDE, P. and CLODE, M. — Effect of BCG infection on leukemia and polyoma in mice and hamsters. Proc. Soc. Exper. Biol. Med., *111*: 739-42, 1962.

46 — ———. — Influence of bacille Calmetter-Guérin infection on polyoma in hamsters and mice. Cancer Res., *26*: 585-589, 1966.

47 — LI, M. C., HERTZ, R. and BERGENSTAL, D. M. — Therapy of choriocarcinoma and related trophoblastic tumors with folic acid and purine antagonists. *New Eng. J. Med., 259*:66-74, 1958.

48 — LI, M. C., HERTZ, R. and SPENCER, D. B. — Effect of Methotrexate therapy upon choriocarcinoma and chorioadenoma. *Proc. Soc. Exper. Biol. and Med., 93*:361-66, 1956.

49 — LUCHERINI, T. — Tentativo di cura della leucemia con inoculazione di sangue infetto di "Plasmodium vivax". *Il Policlinico, 32*:1745-47, 1925.

50 — LUISI, A., DE PADUA BERTELLI, A., MACHADO, J. C., and ACHE DE FREITAS, J. P. — "Linfoma Africano" em Crianças Brasileiras. *Revista Brasileira de Cirurgia, 49*:280-95, 1965.

51 — MACFIE, J. W. S. — An observation on the effect of malaria in leukemia. *Ann. Trop. Med., 13*:347, 1920.

52 — NADEL, E. M., GREENBERG, J., and COATNEY, G. R. — The effect of malaria (*Plasmodium Berghei*) on leukemia L1210 in mice. *J. Infec. Dis., 95*: 109-113, 1954.

53 — NGU, V. A. — The African lymphoma (Burkitt tumour): Survivals exceeding two years. *Brit. J. Cancer, 19*:101-07, 1965.

54 — ———. — Clinical evidence of host defences in Burkitt Tumour. *IN*: J. H. Burchenal, and D. Burkitt, (eds.), Treatment of Burkitt's Tumor. *OP. CIT.*

55 — ———. — Clinical experience in the therapy of Burkitt tumour. *IBID.*

56 — O'CONOR, G. T. and DAVIES, J. N. P. — Malignant tumors in African children; with special reference to malignant lymphoma. *J. Pediat., 56*:526-35, 1960.

57 — O'CONOR, G. T., and RABSON, A. S. — Herpes-like particles in an American lymphoma (preliminary note). *J. Natl. Cancer Inst., 35*:839, 1965.

58 — O'CONOR, G. T., RAPPAPORT, H. and SMITH, E. B. — Childhood lymphoma resembling "Burkitt tumor" in the United States. *Cancer, 18*:411-17, 1965.

59 — OETTGEN, H.F., BURKITT, D., and BURCHENAL, J. H. — Malignant lymphoma involving the jaw in African children: Treatment with Methotrexate. *Cancer, 16*:616-25, 1963.

60 — OETTGEN, H. F., CLIFFORD, P., and BURKITT, D. — Malignant lymphoma involving the jaw in African children: Treatment with alkylating agents and Actinomycin D. *Cancer Chemother. Rept., 28*:25-35, 1963.

61 — OLD, L. J., BENACERRAF, B., CLARKE, D. A., CARSWELL, E. A. and STOCKERT, E. — The role of the reticuloendothelial system in the host reaction to neoplasia. *Cancer Res., 21*: 281-1300, 1961.

63 — OLD, L. J., CLARKE, D. A., and BENCERRAF, B. — Effect of Bacillus Calmette-Guérin (B.C.G.) infection on transplanted tumours in the mouse. *Nature, 184*:291-92, 1959.

63 — ———. — Mengo virus infection in bacillus Calmette-Guérin or Zymosan treated mice. *Fed. Proc., 19*:208, 1960.

64 — ———. — Reticuloendothelial function in various strains of mice. *Proc. Am. Assoc. Cancer Res., 3*:139, 1960.

65 — ———. — and GOLDSMITH, M. The reticuloendothelial system and the neoplastic process. *Ann. N. Y. Acad. Sci., 88*:264-80, 1960.

66 — OSUNKOYA, B. O. — The effect of some anticancer agents and steroid hormones on Burkitt cells in vitro. *IN*: J. H. Burchenal and D. Burkitt, (eds.), Treatment of Burkitt's Tumor. *OP. CIT.*

67 — ————. — The preservation of Burkitt tumour cells at moderately low temperature. *Brit. J. Cancer, 19*:749-53, 1965.

68 — ————. — Various aspects of the Burkitt tumor cell in tissue culture with reference to host defenses. *IN*: J. H. Burchenal and D. Burkitt, (eds.), Treatment of Burkitt's Tumor. *OP. CIT.*

69 — PULVERTAFT, R. J. V. — A study of malignant tumours in Nigeria by short term tissue culture. *J. Clin. Path., 18*:261-73, 1965.

70 — ————. — The use of tissue culture in the diagnosis of Burkitt's tumour. **IN**: J. H. Burchenal and D. Burkitt (eds.), Treatment of Burkitt's Tumor, *OP. CIT.*

71 — ROSENOW, G. — Ueber die Behandlung der leukämie mit impfmalaria. *Deutsche Med. Wchschr., 53*:617, 1927.

72 — ————. — Ueber die Beziehungen der malaria zur leukämie. *Ibid., 44*: 1070, 1918.

73 — SCHUPFER, R. — Studi sulle leucemie e sulle pseudoleucemie. Nota II. L'influenza che sulla leucemia esercitano le mallattie infettive intercorrenti ed il suo valore terapeutico. *Il Policlinico. 12*:145, 1905.

74 — SELAWRY, O. S. — Therapeutic index of methotrexate as related to dose schedule and route of administration in children with acute lymphocytic leukemia. *Proc. Am. Assoc. Cancer Res., 6*: 57, 1965.

75 — SKIPPER, H. E. — Some types of quantitative and kinetic information worth seeking and considering in the design of therapeutic trials. *IN*: J. H. Burchenal and D. Burkitt, (eds.), Treatment of Burkitt's Tumor, *OP. CIT.*

76 — SKIPPER, H. E., SCHABEL, F. M. Jr., and WILCOX, W. S. — Experimental evaluation of potential anticancer agents. XIII. On the criteria and kinetics associated with "curability" of experimental leukemia. *Cancer Chemother. Rep., 35*:1-111, 1964.

77 — STANLEY, N. F., WALTER, M. N. I., LEAK, P. J. and KEART, D. — The association of murine lymphoma with Reovirus type 3 infection. *Proc. Soc. Exper. Bio. Med., 121*:90-96, 1966.

78 — STEINKULLER, C. and BURTON, D. — Immunology of spontaneous mammary tumors in mice. Mode of action of a tumor protective fraction of tubercle bacilli (MER). *Proc. Am. Assoc. Res., 7*:68, 1966.

79 — STEWART, S. E., LOVELACE, E., WHANG, J. and LANDON, J. — A herpeslike virus in lymphoma cells in culture. *Ibid., 6*:62, 1965.

80 — TEN SELDAM, R. E. J., COOKE, R. and ATKINSON, L. — Childhood lymphoma in the territories of Papua and New Guinea. *Cancer, 19*:437-46, 1966.

81 — TRAGER, W. — Inhibition of Tumor I of chickens by simultaneous infection with the malaria parasite *Plasmodium Lophurae. Fed. Proc., 10*:373-74, 1951.

82 — ——————. — and MCGHEE, R. B. — Inhibition of chiken Tumor I by plasma from chickens infected with avian malaria parasite. *Proc. Soc. Exper. Biol. Med., 83*:349-52, 1953.

83 — WEIGLE, W. O. — Induction and termination of immunologic tolerance to protein antigens. *Fed. Proc., 25*:160-164, 1966.

84 — WEISS, D. W., BONHAG, R. S., DeOME, K. B. — Protective activity of fractions of tubercle bacilli against isologous tumours in mice. *Nature, 190*:889-91, 1961.

85 — WILLIAMS, M. C. — Implications of the geographical distribution of Burkitt's lymphoma. *IN*: J. H. Burchenal and D. Burkitt, (eds.), Treatment of Burkitt's Tumor, *OP. CIT.*

86 — WRIGHT, D. H. — The gross and microscopic pathology of Burkitt's tumor.

87 — ZIEGLER, J. L. and MILLER, D. G. — Lymphosarcoma resembling the Burkitt tumor in a Connecticut girl. Submitted to J.A.M.A., 1966.

88 — ZUELZER, W. W. — Implications of long-term survival in acute stem cell leukemia of childhood treated with composite cyclic therapy. *Blood, 24*: 477-94, 1964.

revista brasileira de cancerologia

índice

abril, 1968 — guanabara — brasil

ÓRGÃO OFICIAL DO SERVIÇO NACIONAL DO CÂNCER