JUAN A. DEL REGATO, M.D.
JANEWAY LECTURER, 1973

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INTRODUCTION OF JANEWAY LECTURER 1973*

By MILFORD D. SCHULZ, M.D.
Chairman, Janeway Lecture Committee
BOSTON, MASSACHUSETTS

Each year since 1933 this Society has sponsored a special Lecture, the purpose of which is dual. First, to recognize the contributions to our understanding of cancer made by an outstanding physician or scientist of the here and now, chosen by a special Committee of the Society. The second purpose of the Lectureship is to do honor to those scientists and physicians past upon whose shoulders we all stand. Although these Lectures have been known as the Janeway Lecture—after Dr. Henry Harrington Janeway, a New York physician and founder of this Society and an American pioneer in the use of Radium—the intent of this commemoration is truly more catholic than for just one man, and indeed, like the very name of this Society "The American Radium Society" is but a bit of verbal history—a shibboleth—indicative of true purpose.

So once again your Committee has carefully given ear to the advice of our emissaries, Hugin and Munin which appear in the heraldry of this Society, and have chosen as the one who will once again take us for a draught at the Well of Mimir—Juan del Regato, presently Director of the Penrose Cancer Hospital in this city. The Ravens may have been influenced in this recommendation by this name, for Mimir's Well, being a well of knowledge, is by definition not a static but a flowing well and a flowing well is often the source of a brook or stream, and del Regato being translated means from or of the brook.

Our Lecturer of this year started his career in 1909 by being born in the provincial Cuban community of Camagüey into a humble family of Spanish and Mayan origins.

His early formal education started in the town of his birth and was continued under private tutelage in the port of Nuevitas to which his family had, because of greater opportunity, moved, and then for a while, because of political disturbances in Cuba, in his mother's ancestral home of Mérida, Yucatán. When the political climate in Cuba improved, the Regato family returned to Cuba—to the larger community of Santa Clara—where young Juan completed his primary schooling.

During these early years, a number of circumstances occurred which I believe were formative of young Juan's future. Señor Juan del Regato—the father—among other things ran the local photography shop and was the projectionist at a motion picture theater. This movie house

* Presented at the Fifty-fifth Annual Meeting of the American Radium Society, Colorado Springs, Colorado, April 22-26, 1973.

was no great palace but a modest place of entertainment where 3-4-5 reels were shown from a single piece of projection equipment. This of course meant shutting down the show every time a reel had to be changed. To keep the audience occupied during these changes, it was young Juan's job to show lantern slides—and so started an occupation from which he has never recovered.

Another incident which helped mould the young Juan Angel was when at the age of 10 he was selected from his fellow students at the Santa Clara School to give a special speech on an occasion of considerable importance—the day celebrating Cuba's freedom from Spanish Rule. This was a portent for the future which has extended to today.

But perhaps the most indelible of all was the fact that the town of his birth was also the place of birth of an earlier great physician, Dr. Carlos J. Finlay, of worldwide reputation as one of the principals in the conquest of yellow fever. Juan never tired of hearing from the lips of his parents the story of this great man and early resolved to pattern his own life after his—to become a physician.

And so it transpired that in 1926 young Juan registered for the 7 year course in Medicine at the University of Havana. This meant much sacrifice for his family and hard work for the young man himself. His assiduous application to the work at hand and the fact that he had learned something about photography from his father attracted favorable attention from the Director of the Cancer Hospital attached to the University and he was offered and accepted a job in the X-ray Department, thus opening new doors to his growing experience. Political fate, however, struck again and before he could complete his medical training, the University was closed. The contacts he had made in the Cancer Hospital now stood him in good stead. The Cuban Cancer League saw promise in this young student and decided to sponsor his continued education abroad and so it was that young doctor-to-be del Regato went to France where he completed his medical training at the University of Paris in 1934 and consolidated his already determined resolve to pursue a career devoted to work in the field of Cancer.

Following graduation he was given a Fellowship at the Fondation Curie where he came under the influences of those whose names are legendary in Radiotherapy and Cancer Control—Regaud, Lacassagne, Coutard, whose assistant he became. He remained at the Fondation in this capacity till 1938, when Dr. Max Cutler prevailed upon Dr. Coutard to join him at the Chicago Tumor Institute. When Dr. Coutard went to Chicago, he took his promising young assistant with him and this is how Dr. Juan A. del Regato came to the USA where he became a naturalized citizen in 1941.

I didn't know it then and neither did Juan but in those days we worked within a short distance of each other—he at the Chicago Tumor Institute with Dr. Cutler, a Senior member of this Society, and Simeon Cantril and Franz Buschke, both past Janeway Lecturers, and I at Northwestern University with the late Dr. James Case, also a past Janeway Lecturer and past President of this Society.

Chicago was followed by 5 years of the practice of Radiotherapy and related research at the Garfield Hospital in Washington, D. C., and as a Research Fellow of the National Cancer Institute in Baltimore.

Now it happened that one day during this Washington phase of his life, there came out of Galva, Illinois, a young nurse named Inez to see the sights of the Nation's capital. Something must have already gone on between these two during Juan's Chicago days for he offered to show her the town. Never one to misuse an opportunity, Juan during the course of the day mentioned that he had in his pocket an interesting document and would the young lady like to see it? She would and this document just happened to be a marriage license—and so it came to pass that yet another milestone in Vita Regato was accomplished. To this union there came 3 children.

After Washington there came 6 years as Chief of Radiotherapy at the Ellis Fishel Cancer

Hospital in Columbia, Missouri. It was at the Ellis Fishel that he developed a lasting association with Dr. Lauren Ackerman, your Janeway Lecturer of 2 years ago, and with whom he wrote what has come to be a standard reference and classic in the American Cancer Literature. It was here, too, that he started his still larger family—a family that still today he fathers in ever increasing numbers—the children of his mind and soul, his trainees—who now number in the dozens and for whom, even if all else is forgotten, he will always be honored and remembered.

Since 1949, del Regato has been Medical Director of the Penrose Cancer Hospital of this city—the story of how this all came about is a tale of its own. It is here that he has come into full flower. Emerson wrote that if a man write a better book—preach a better sermon—build a better church organ or make a better mouse trap—though he build his house in the wilderness, the world will beat a path to his door.

Colorado Springs is not quite a wilderness, but certainly the path to Dr. del Regato's door is widely known and well worn.

The many accomplishments of our Lecturer are too well known and the honors accorded him too many and too much a matter of record to recount here. Sufficient to say, that it gives me the greatest personal pleasure to, on behalf of the Janeway Lecture Committee, introduce as the 38th Lecturer Juan Angel del Regato, M. D., Sc. D., respected physician, widely read and known author and authority on clinical cancer management, beloved teacher, historian, political-social and moral philosopher, who will speak to us on "Total Body Irradiation in the Treatment of Chronic Lymphogenous Leukemia."

TOTAL BODY IRRADIATION IN THE TREATMENT OF CHRONIC LYMPHOGENOUS LEUKEMIA*

JANEWAY LECTURE, 1973

By JUAN A. DEL REGATO, M.D., Sc.D.†
COLORADO SPRINGS, COLORADO

IN March 1902, William Allen Pusey, a pioneer American radiotherapist and dermatologist, co-author of one of our earliest books on roentgentherapeutics, received from Dr. Jacob Frank, of Chicago, a referred patient with a diagnosis of leukemia: the 44 year old man had voluminous lymphadenopathies of the neck, axillae and groins (Fig. 1), plus enlargement of the spleen and liver; in addition he presented 74,000 white cells per mm.^{3}, 80 per cent of which were lymphocytes, in the circulating blood. Roentgen therapy was administered on a daily basis; the lymph nodes regressed notably within the first 2 days, the spleen diminished in size and the white cell count came down to normal limits (Fig. 2), but irradiations were continued for 3 weeks producing epilation and dry epidermitis.[41] One year later, Nicholas Senn, a Chicago surgeon, reported his experience with roentgentherapy in a case of leukemia.[44]

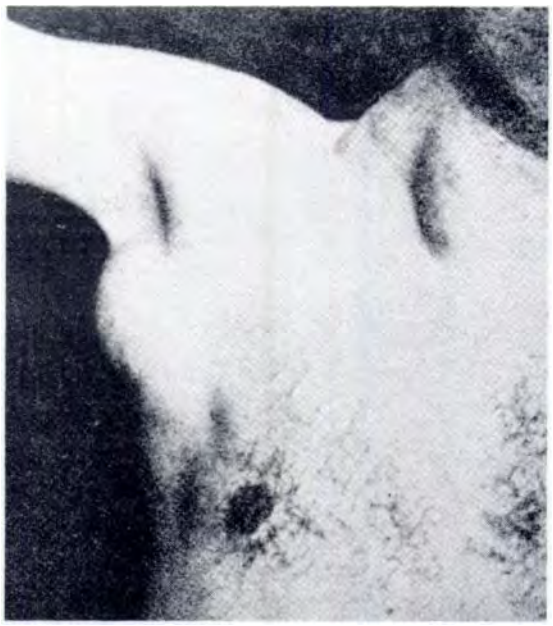

FIG. 1. Patient with cervical and axillary lymphadenopathies from chronic lymphogenous leukemia, irradiated by Dr. William A. Pusey, of Chicago, in March, 1902.[41]

In 1903, Efim S. London, of Berlin, published the sequence of observed events following total body irradiation of lower animals.[27] Also in 1903, H. Heineke, of Leipzig, produced his masterfully detailed histologic studies of the effects of radiations on the tissues of experimental animals.[16,17] Heineke's description of the radiation effects on lymphoid tissue has never been surpassed; he also noted the bone marrow's ability to recover. In 1904, Charles Aubertin and E. Beaujard, made observations, in Paris, on the effects of irradiations on the blood of leukemics.[3] In 1906, Alfred S. Warthin, of Ann Arbor, studiously verified and extended Heineke's reported effects of irradiation on the blood forming organs.[50]

Friedrich J. Dessauer, Frankfurt's pioneer biophysicist, proposed in 1905, the irradiation of the entire human body (Fig. 3) by means of 3 low voltage roentgen-ray sources operating simultaneously.[12] But early enthusiasts of whole body irradiation must have been deterred by poor results and by the untoward effects on the hemopoietic system. In 1923, Henry Chaoul, of Berlin, reported his early trial of *teleroentgentherapy* in Hodgkin's disease.[6] In 1925, Werner Teschendorf, of Cologne, initiated his work which was followed by his long sustained advocacy of total body roentgentherapy for the treatment of polycythemias,

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lymphoid tumors and leukemias.[47,48] Concurrently, Torleif Dale of Oslo, also applied this approach, with a higher daily dose, for the treatment of leukemias.[9] In May, 1931, Arthur C. Heublein, of Connecticut, started work in a specially built unit for the continuous and simultaneous total irradiation of 4 patients at the rate of 1.25 r per hour.[18] The Heublein unit, built at the Memorial Hospital of New York under specifications of Gioacchino Failla, provided for continuous irradiation with automatic interruptions for visits by physicians, nurses and attendants (Fig. 4; and 5); the patients received about 350 r in 12 days and sometimes more. Heublein died prematurely in the course of this experiment; posthumously, his colleagues reported on its results on a variety of cases which included 27 patients with lymphogenous leukemia.[8] At the same time Traian Leucutia[23] of Detroit, made a serious analysis and defense of the relative advantages of regional radiotherapy.

In the 1930s the work of Teschendorf motivated a wave of enthusiasm for sub-

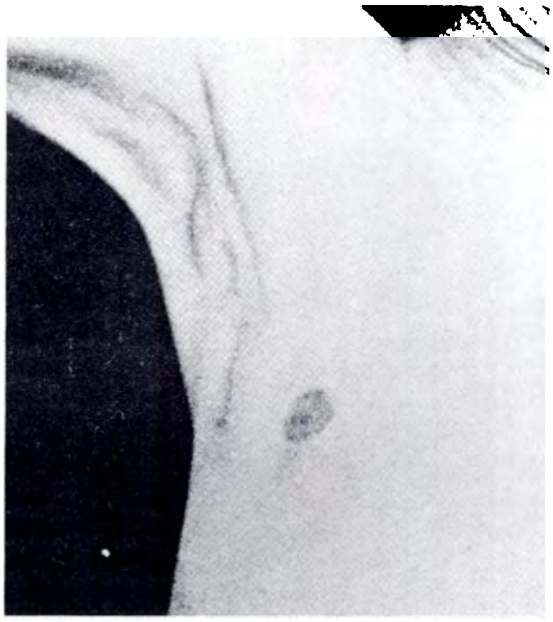

Fig. 2. Same patient following irradiation showing regression of lymphadenopathies and epilation of the axilla and chest.[41]

total and total body irradiation in various countries of Europe: Auguste Devois[13] and Lucien C. M. Mallet[29] in France, Max

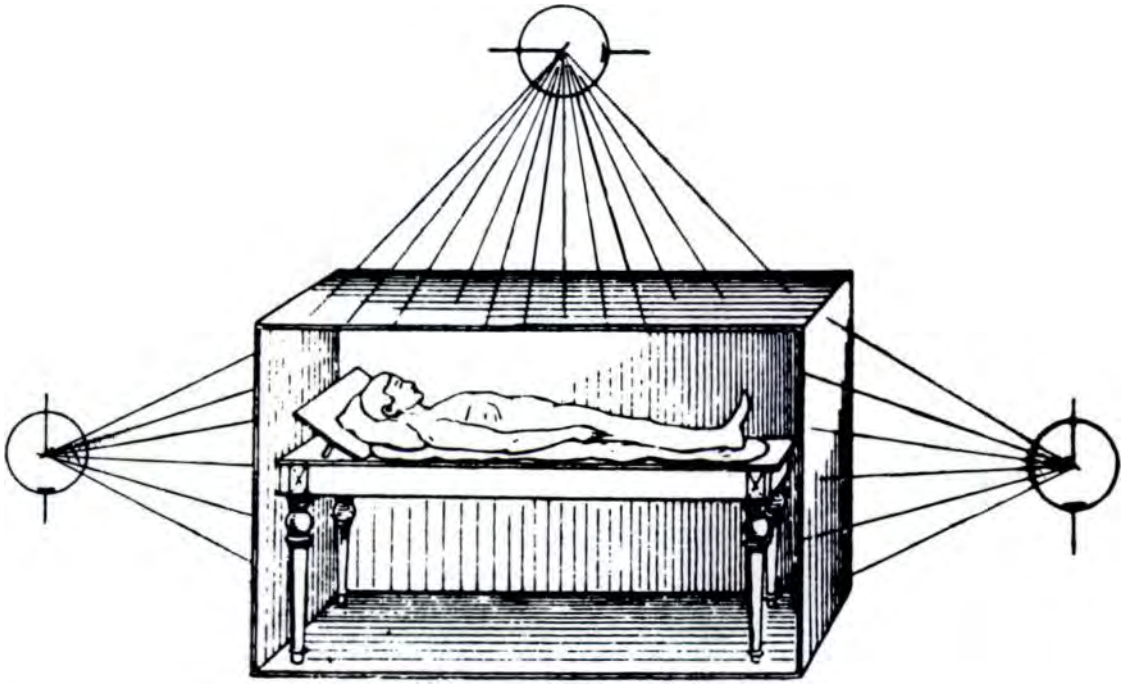

Fig. 3. Scheme for total body roentgen therapy with 3 sources as suggested by Friedrich J. Dessauer of Frankfurt, in 1905.[12]

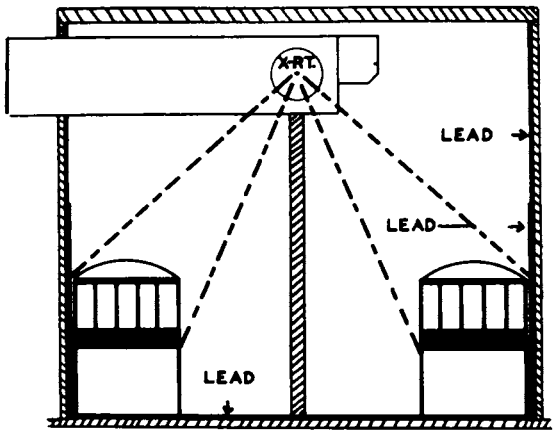

FIG. 4. Sketch of the Heublein unit for continuous total body irradiation of 2 patients simultaneously.[8]

Sgalitzer[45] in Austria, Felix Sluys[46] in Belgium and many others,[40] variously tried and reported their results in cases of generalized carcinomatosis as well as of malignant lymphoid tumors and leukemias. Joseph Belot[4] in France and H. Fuhs[15] in Germany, treated generalized dermatoses with total body irradiation. Gian Giuseppe Palmieri[38] of Bologna, favored, as Heublein, the continuous irradiation of confined patients; Pierre Xavier Marquès[30] of Toulouse, utilized simultaneous irradiation from twin tubes for homogeneous distribution throughout the body. P. Jacob[19] of Nancy, proposed the irradiation of patients in a moving bed, a method that he called *cineroentgentherapy*. Daniel den Hoed[11] of Rotterdam, and others became discouraged by the hemopoietic injury resulting from the latent effects of what appeared to be relatively small doses. A review of 270 cases of total body irradiation, including 72 cases of chronic lymphogenous leukemia, treated during the decade, was published by Frederick G. Medinger and Lloyd F. Craver.[32]

In the 1940s the tragic events of Hiroshima and Nagasaki triggered attention to the consequences of total radiation exposure; the survivors of the holocaust offered sad evidence of various degrees of somatic effects of a single massive exposure to radiations.[25] Experimental researchers, by the hundreds, undertook anew to study the radiation effects of various tissues and organs, repeating, often without gain, the overlooked or forgotten experimental work of the pioneers.[22] Accidental irradiation of atomic scientists added to the recorded evidence of the lethality of relatively small amounts of radiations, when received in a short time by the entire body.[20]

In the 1950s total body irradiation was advocated in the management of acute leukemias as a preliminary step to total bone marrow replacement.[5,31] The procedure was well founded on experimental evidence of success in lower animals, but it was seldom successful in man; moreover, the increasing effectiveness of chemotherapy in the acute leukemia of children was soon to retire these efforts. Concurrently, Edwind E. Osgood, of Portland, Oregon, persistently emphasized the value of total body

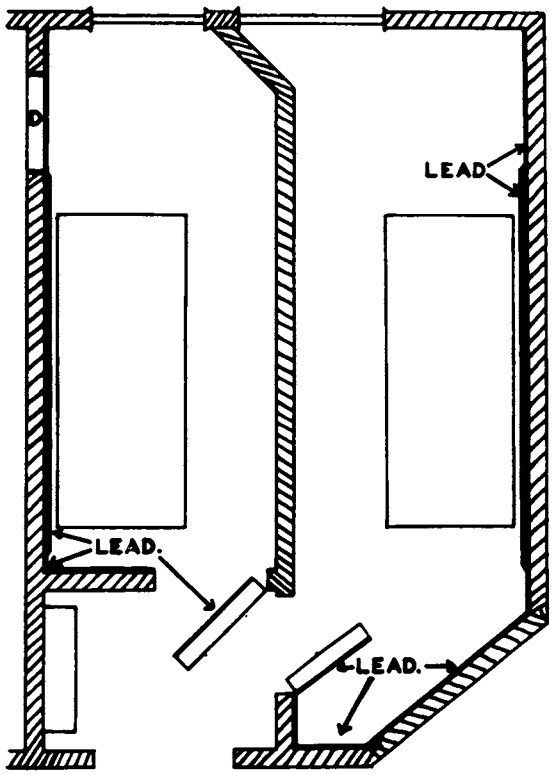

FIG. 5. Floor plan of the Heublein unit designed by Dr. Gioacchino Failla for the Memorial Hospital of New York City.[8]

("spray") roentgen therapy and of radioactive phosphorus administered at regular intervals ("titrated") in the management of chronic leukemias.[36,37] Vincent P. Collins and R. Kenneth Loeffler[7] investigated again the possibilites of single dose total body irradiation; E. Richard King continued to utilize total body irradiation in the treatment of generalized malignant tumors.[21] Cobalt 60 units began to be utilized for these purposes and special rooms were designed for the utilization of radioactive cesium 51. It is of interest that those who advocate total or subtotal body irradiation of generalized malignant tumors,[26,48] often invoke an indirect effect to explain the beneficial results of small doses.

In the 1960s, it was in the expectation of temporary suppression of the lymphoid and reticuloendothelial tissues, for the purpose of suppressing the immunologic rejection of transplanted tissues, that total body irradiation was again sought.[33,49] And here again this aid was soon renounced in favor of effective drugs. A contemporary interest in total body irradiation comes under the aegis of Civil Defense.[24,42,43]

RADIOPATHOPHYSIOLOGY

Most of our knowledge of hematologic radiation effects is based on the results of experimental, massive, single dose total body irradiation of lower animals; the usually referred to LD_{50} is found from such single exposure experiments. Friedrich Ellinger[14] showed that simple fractionation decreased the mortality rate of a given total body dose. A. H. Pontifex and Leonard F. Lamerton[39] studied the hematologic response of rats to repeated total body irradiations at rates ranging from 15 to 200 r per day; they found a more rapid mortality for the higher doses, and a lesser damage or a greater ability to recover with the lower dose rates. It must be borne in mind that the time sequence may be quite different in lower animals than in man because of the differences in the cell kinetics of the hemopoietic cell-renewal systems.

The victims of the atomic bomb and the accidentally irradiated atomic scientists suffered also from a single massive exposure. Patients irradiated in anticipation of bone marrow replacement or organ transplants were usually exposed to one or two sublethal doses of radiations. A more or less intense syndrome ("radiation sickness") definitely dose related, may be observed in man; it consists of nausea, vomiting, fatigability, listlessness and diarrhea.[2] Lowell S. Miller and associates[34] found these symptoms practically absent below a single exposure of 100 r, but rather importantly disturbing in those receiving 200 r.

Although the irradiation may be simultaneous, the facts observed in the peripheral blood do not occur simultaneously for they result from the effects on different hematopoietic cell lines with their own dynamic balance. Half a century ago, George R. Minot and Roy G. Spurling[35] made a collective study of 42 patients with various forms of cancer, regionally irradiated with rather large fields. In patients in whom they observed relative leukopenia they found its extent and the patients recovery directly related to the size of the field of irradiation and to the dose administered. Maurice Tubiana and Claude M. Lalanne[49] contrasted the hematologic effects observed in patients who received 400 r or 100 r (Fig. 6) at one sitting: the drop in the numbers of total leukocytes, of lymphocytes and platelets, which occurred in both, was faster for the larger dose; recovery was manifest after the third week, but it was more vigorous in patients receiving the smaller dose. James Adelstein and James B. Dealy, Jr.[1] studied 6 patients who received an initial total body dose of 250 r; they found the *half-reduction time* for lymphocytes to be 4 days, for granulocytes 6 days, for reticulocytes 10 days and for platelets 16 days. There are no studies available of the effects of fractionated total body irradiation of normal persons over a period of weeks or months.

MATERIAL AND METHOD

Our experience with total body irradia-

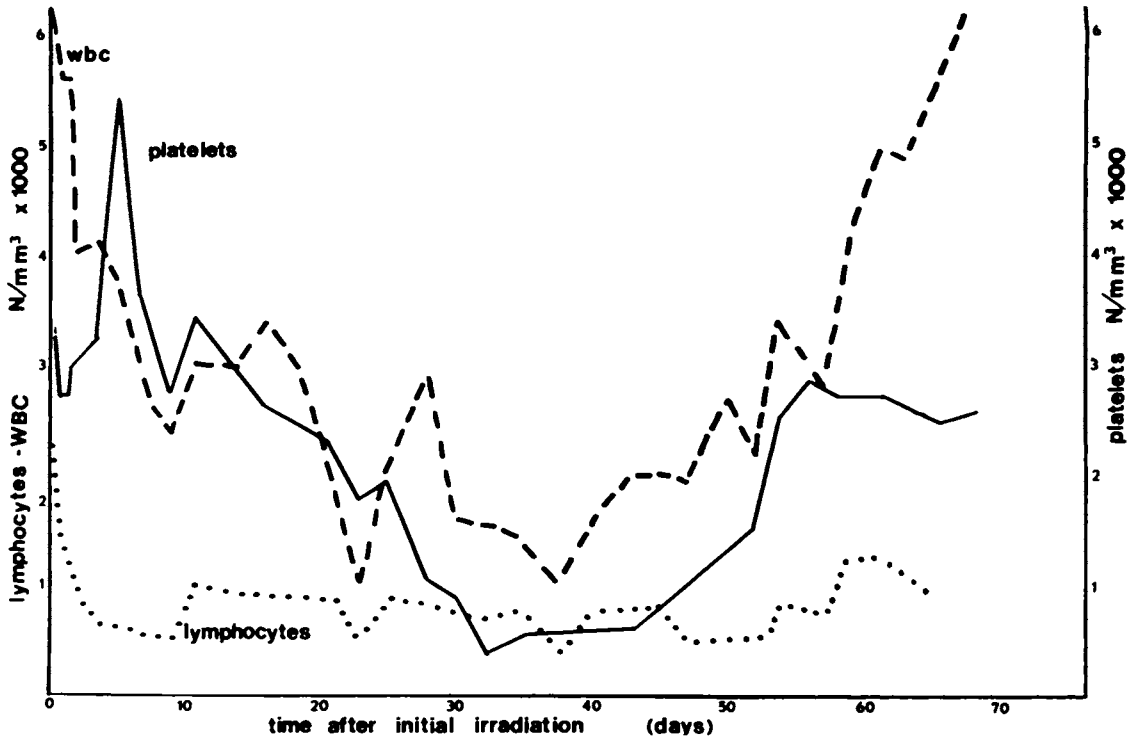

FIG. 6. Peripheral blood changes observed in a normal individual submitted to a single total body irradiation of 100 r (from Tubiana and Lalanne[49]).

tion of patients with chronic lymphogenous leukemia is reported here for the first time. We carried out total body irradiation in the late 1930s, but have lost contact with the patients' records. This report is based on 15 patients irradiated at the Ellis Fischel Cancer Hospital of Columbia, Missouri, from 1943 to 1948, and on 46 additional patients treated at the Penrose Cancer Hospital of Colorado Springs from 1949 to 1969. Thirty-seven of these patients were males and 24 females; the youngest was 43 and the oldest 84 years of age; both the median and average age of these patients was 64 years.

Patients whose treatments were started in the past 3 years are not included in this report, for some are still under treatment. Patients receiving only regional irradiation were excluded. Two patients who died of concurrent metastasizing cancer, one of the bladder and another of the prostate, were not included; 1 who had had cancer of the breast, but who died of leukemia was retained. Two patients with congestive heart failure who could not stand the treatments were eliminated from consideration. Thus, this is a selected series.

In the 30 years of this experience we have diagnosed and followed a number of symptomless patients who received no treatment or only occasional regional irradiation; they constitute a more favorable group than the one subject of this report. The disease is often insidious, but not always slow in its development.

All of the patients had repeated confirmatory bone marrow biopsies. In 8 of our patients, who had started their clinical course with a peripheral lymphadenopathy, a biopsy had been done and a diagnosis of "malignant lymphoma" (lymphocytic, reticulum-cell, histiocytic, lymphoblastic) had been rendered; in 2 patients such diagnosis had been made on a surgical specimen of the cecum. We have long maintained that a diagnosis of malignant lymphoid tumor in a lymph node should be challenged

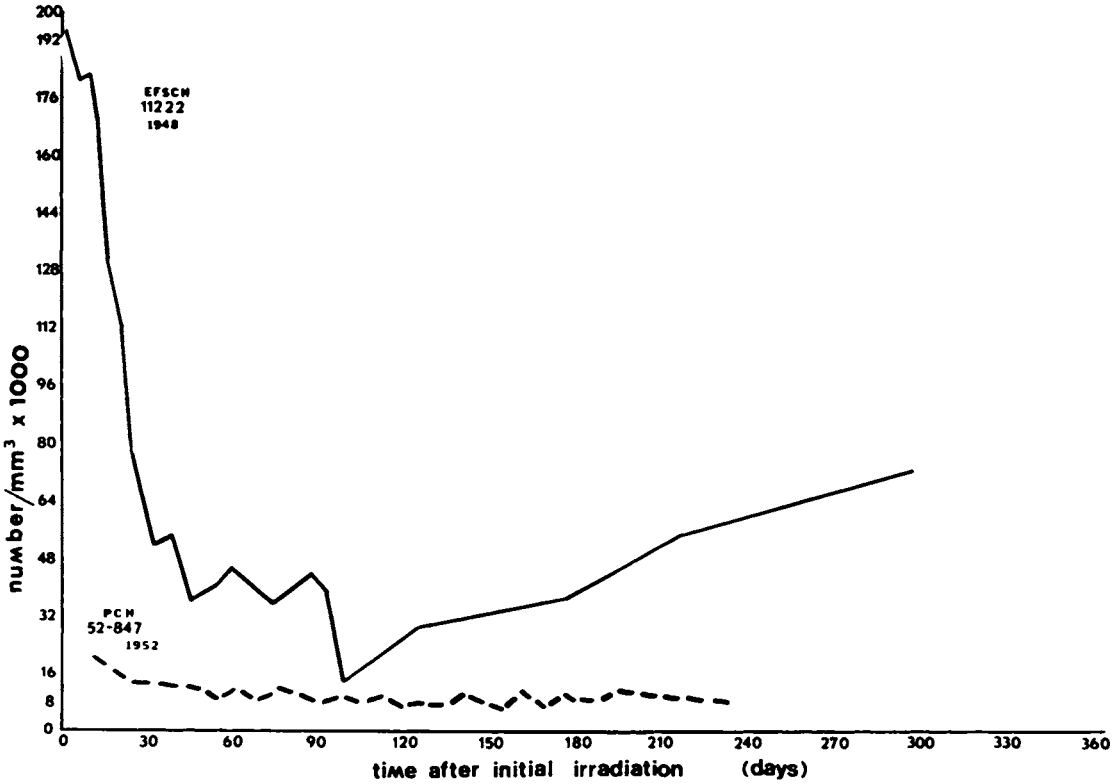

FIG. 7. Observed changes in the total white blood cell count of 2 patients during the first year of irradiation.

if the clinical character and course of the case are at variance with what one expects from generalized lymphosarcomatosis. Advanced age, preserved general condition in spite of large masses and long course, maintained weight, symmetry of lymphadenopathies, etc. should bring suspicion that a histopathologic diagnosis of "malignant lymphoma" is probably in error. The accommodating theory that malignant lymphomas may "turn into a leukemic phase" simply contributes an often convenient white-wash for too categorical an initial diagnosis of tumor, where vacillation would have been justified. Equally accommodating and *unproved* is the concept that lymphosarcoma and leukemia are but colors of the same rainbow. As a result, clinicians everywhere fail to acquire a clear concept of the differences involved and the confusion distorts our statistics of results. In malignant tumors of the lymphoreticular system, clinicians and pathologists have failed to exploit the modifying light of contributory clinical details, as they have in bone tumors; internists seem to expect, and accept without dispute, the morphologists word as definitive. Yet, it remains a fact that without clinical information to help him the histopathologist may be entirely unable to exclude leukemia on a biopsy of a lymph node.

When we began our experience, we chose to deliver a short series of daily total body treatments with the intention of repeating it at long intervals; in other cases we gave smaller amounts daily for several weeks. Some of our earlier patients treated at the Ellis Fischel Cancer Hospital received only repeated discontinued series lasting about 10 days, but no weekly irradiation. Once we became aware of the relative safety of our doses, we decided to start with a series of 10 daily total body irradiations and to

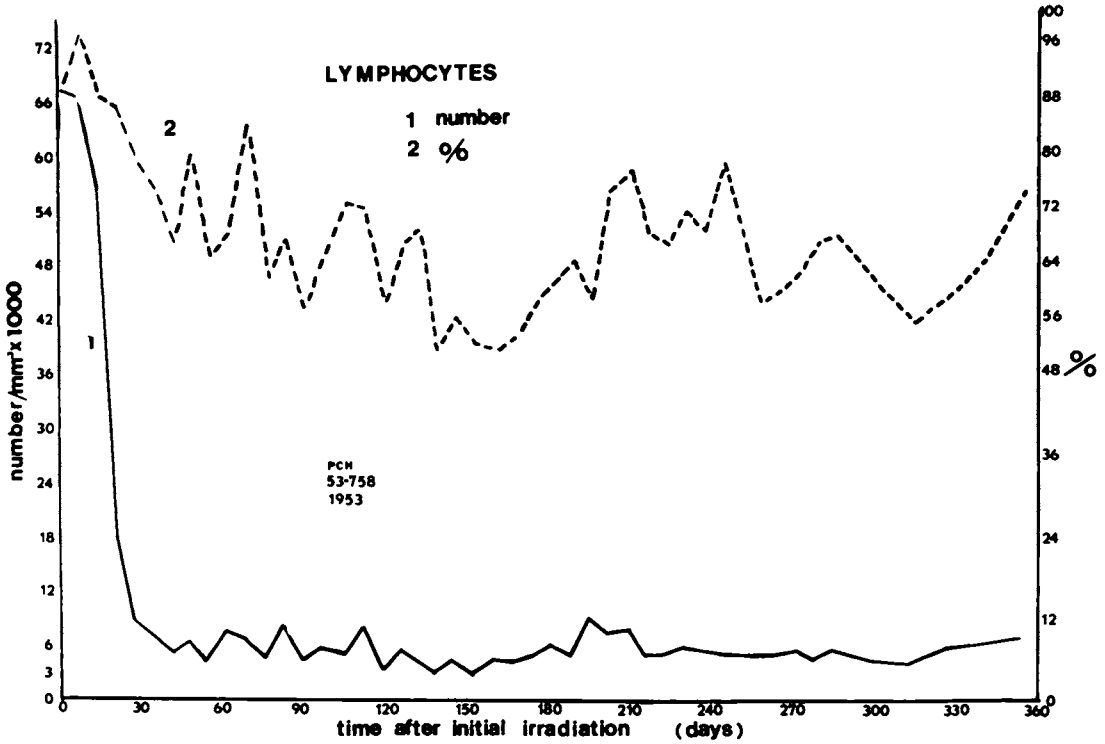

FIG. 8. Although the total number of circulating white blood cells was diminished considerably in this patient during the first year of treatments, the peripheral lymphocytosis persisted.

follow this by a weekly irradiation. In due course we decided to repeat an annual course of the same order as that of the initial series. In summary, our procedure consists of the following:

1. a series of 10 *daily* irradiations of 10 r
2. one *weekly* irradiation of 5 r
3. regional irradiation of spleen or lymph nodes as required
4. an annual "booster" of 10 daily irradiations of 10 r.

Our purpose is to maintain all patients under this regimen *for their life time.* We have found the procedure safe and satisfactory. In this series of patients the total dose received varied, of course, with their survival: the maximum was 2,760 r in $7\frac{1}{2}$ years; another patient received 1,870 r in 6 years; 2 had nearly 1,200 r in 4 years; 6 others received between 900 and 1,100 r in 3 to $3\frac{1}{2}$ years.

For a long time our patients were irradiated at 2.30 m. target skin distance, with a 250 kv. unit, operating at 15 ma. with 2 mm. of copper and 1 mm. aluminum filtration; patients layed recumbent on the floor with their knees flexed and received oblique irradiations frontolaterally, alternating sides for homogeneity. Presently they are irradiated with a cobalt 60 unit, in the sitting position, at 3.10 m. source skin distance. The doses are calculated at the surface of the skin without benefit of back scatter. An integral dose, ideally desirable, is difficult to establish; the distribution of doses in the trunk of a phantom reveal a coefficient of homogeneity of 0.87.

Irradiation of the spleen has often to be done also; it is our feeling that the spleen should be irradiated without waiting for it to become uncomfortably large and subject to infarction. The dose administered to the spleen need not be large, and should not be, to allow for re-irradiation when it becomes necessary again. Irradiation of cervical, axillary, inguinal or abdominal

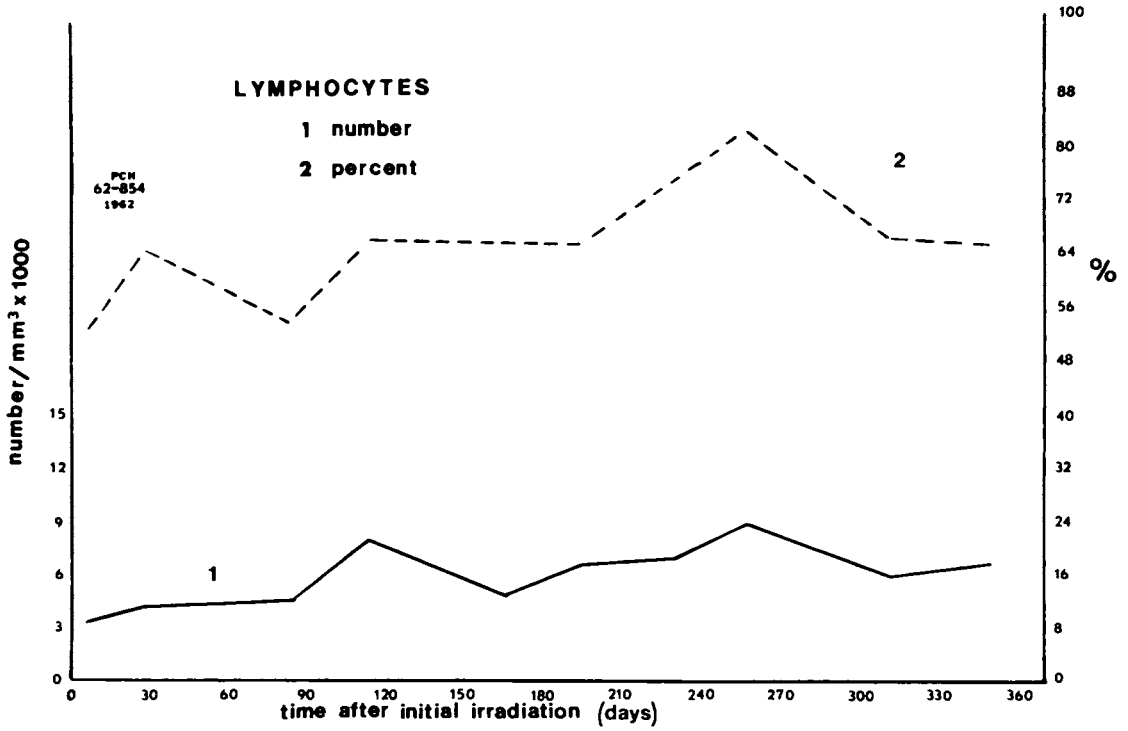

FIG. 9. Total body irradiation of this patient was followed by gradual increase in the number of lymphocytes and in their relative percentage in the peripheral blood cell count.

lymph nodes may also have to be done to eliminate discomfort. Regression of these lymphadenopathies takes place rather promptly and the total dose necessary for complete regression may be less than moderate.

All our patients were kept under close hematologic surveillance, receiving medical treatment as became indicated. Hospitalization and antibiotic therapy were readily available to them, since they are often subject to infections.

RESULTS

Chronic lymphogenous leukemia is an incurable disease; results of treatments can only be evaluated on a relative basis. An expression of "remission" requires definition of a concept of such remission which may be thought self-serving. Very few of our cases had periods in their course when their chronic lymphogenous leukemia was not diagnosable. All of the 61 patients subject of this report have died: the longest survival was *15 years*, the shortest *2 months;* the average was *46 months*, and the median *39 months*. The 5 year survival was 21 per cent (Fig. 12). There were 39 patients with elevated white blood cell counts at the beginning of treatments; their average survival was *51 months*. The 22 other patients had normal or subnormal white blood cell counts in the peripheral blood: their average survival was *38 months*. In 7 patients in whom the differential white blood cell count never showed a percentage of lymphocytes above 50 per cent, the average survival was only *26 months*.

The hemopoietic response, as measured by the peripheral blood cell count revealed a frequent decrease of leukocytes when the original count was high, coming down to normal limits within a few weeks and sometimes below normal; but in other instances the leukocyte count remained high or even increased during the course of treatments (Fig. 7). In patients who presented a normal or subnormal initial white blood cell

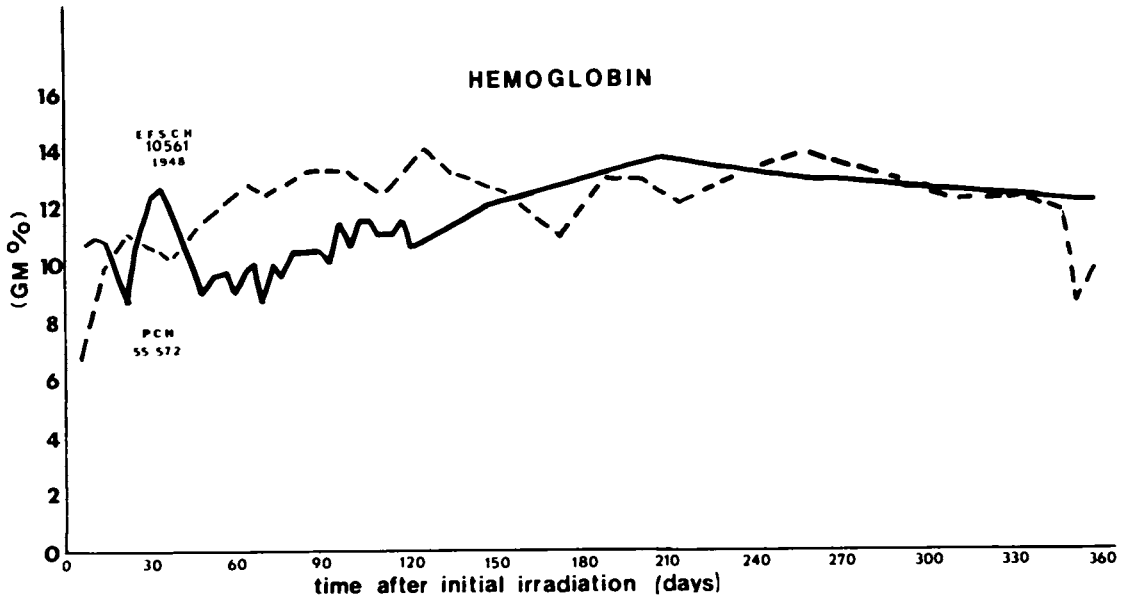

FIG. 10. The hemoglobin was not affected by total body irradiation at therapeutic levels. These 2 curves represent variations observed during the first year in 2 different patients.

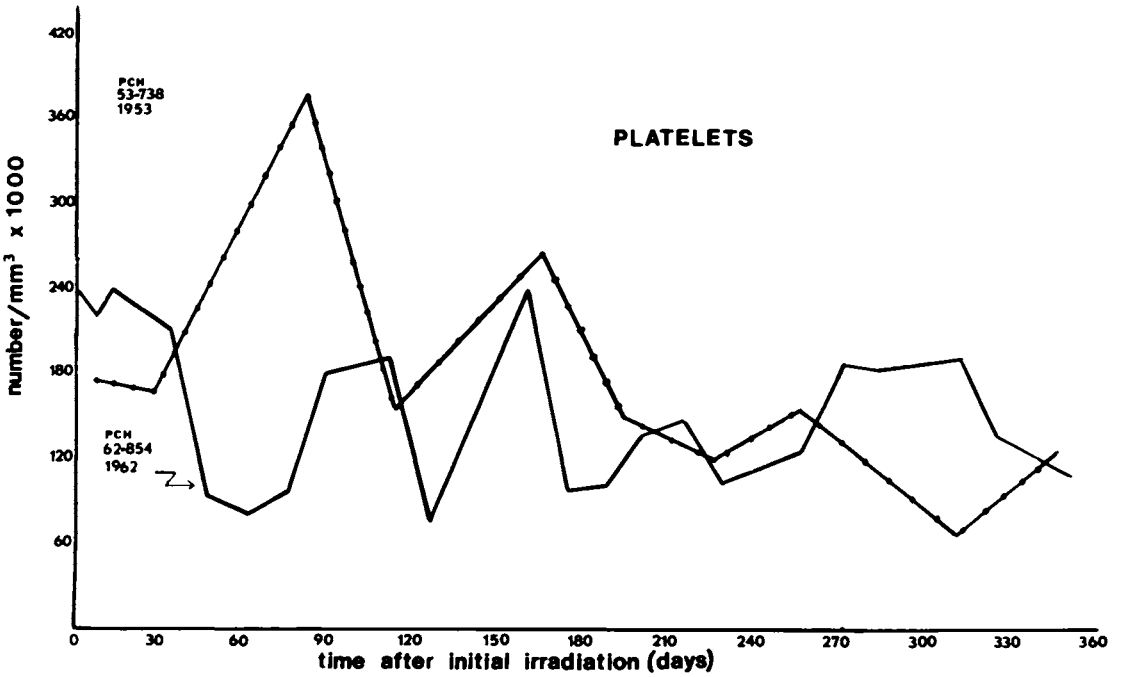

FIG. 11. A gradual decrease in the number of circulating platelets is often observed during the course of total body irradiation, sometimes to very low levels, but without bleeding consequences.

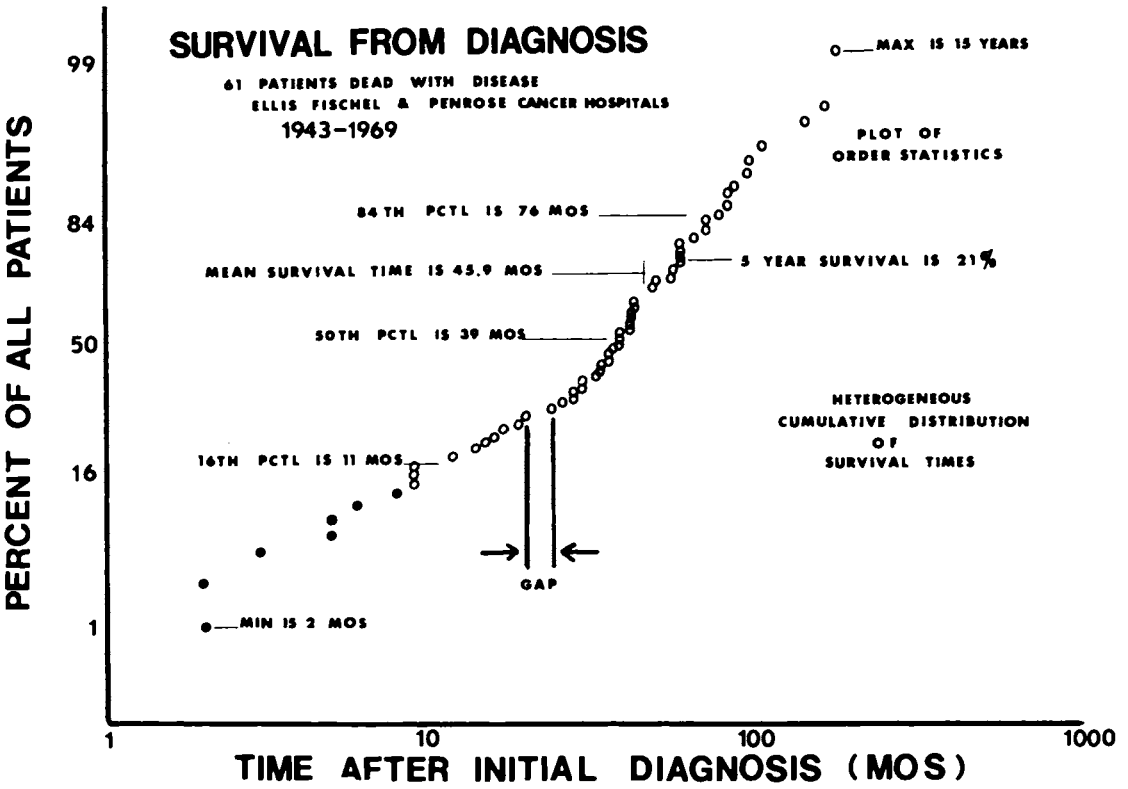

FIG. 12. Cumulative distribution of duration of survival from date of diagnosis. Pooled data of Ellis Fischel State Cancer Hospital (15 patients, 1943–48) and Penrose Cancer Hospital (46 patients, 1949–69).

count there was often a reduction to subnormal levels or no change at all. A high initial percentage of lymphocytes was most often unaffected by irradiations in spite of an absolute decrease of all leukocytes (Fig. 8). Some patients who had an initial normal percentage of lymphocytes underwent a gradual increase to high levels (Fig. 9). In

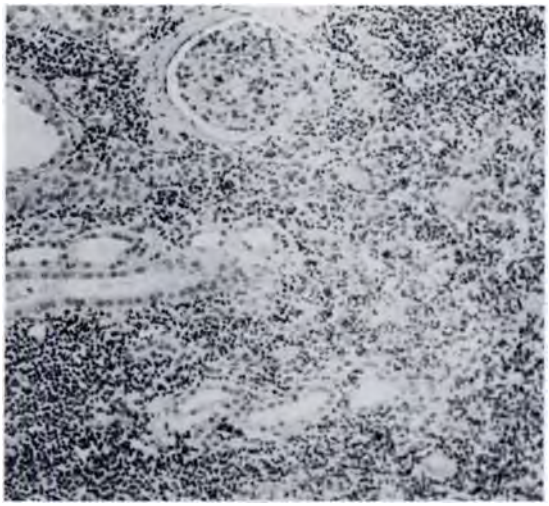

FIG. 13. Extensive infiltration of kidneys is frequent. Routine mild irradiation of these organs may be as justifiable as the irradiation of the spleen.

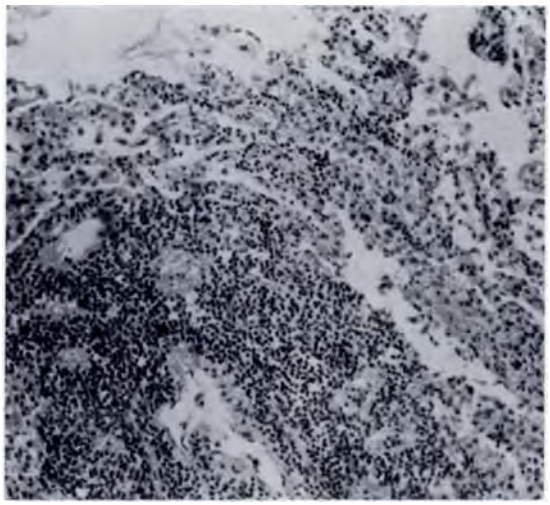

FIG. 14. Infiltration of the lung is frequently found at autopsy and may be in part responsible for the frequent death through pneumonia.

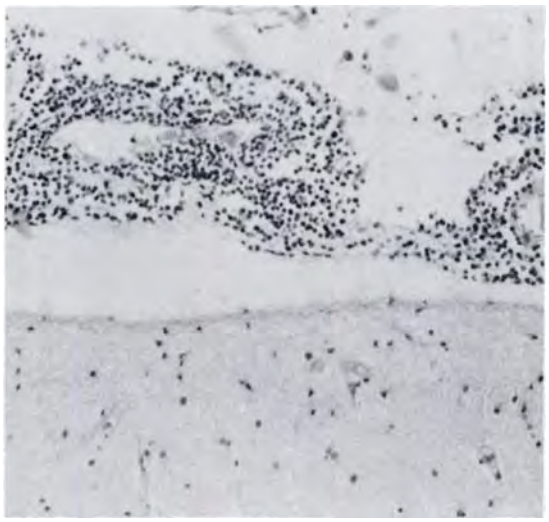

Fig. 15. Meningeal infiltration by chronic lymphogenous leukemia. Intracranial manifestations may mimic a stroke.

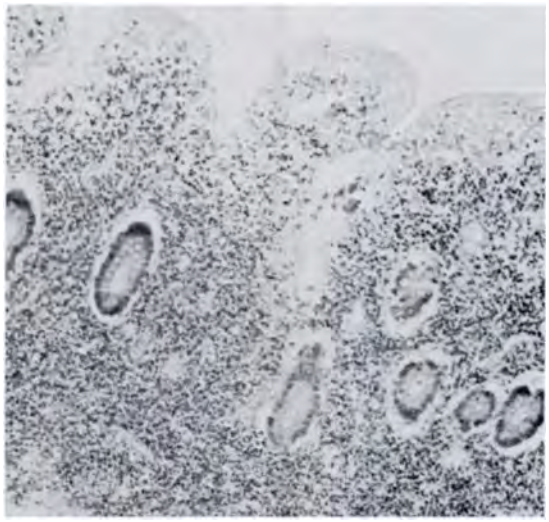

Fig. 17. Leukemic infiltration of the small intestine may suggest a primary tumor of that area. The same is true of the cecum.

a few cases the normal percentage of lymphocytes or the lymphopenia persisted or became worse. In very few cases the initially normal hemoglobin or hematocrit came down (Fig. 10); some patients necessi-

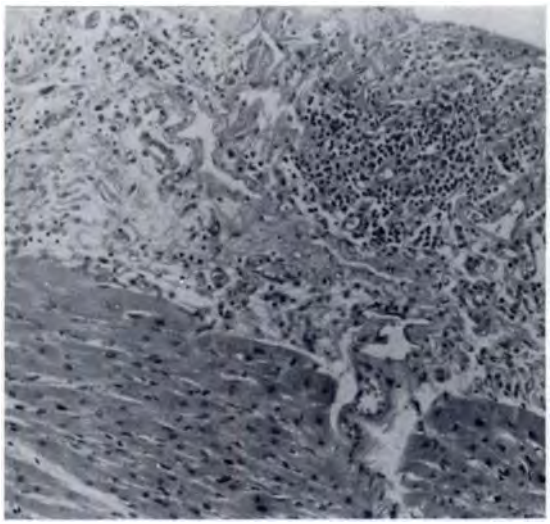

Fig. 16. Pericardial infiltration leads to effusion and possible tamponade.

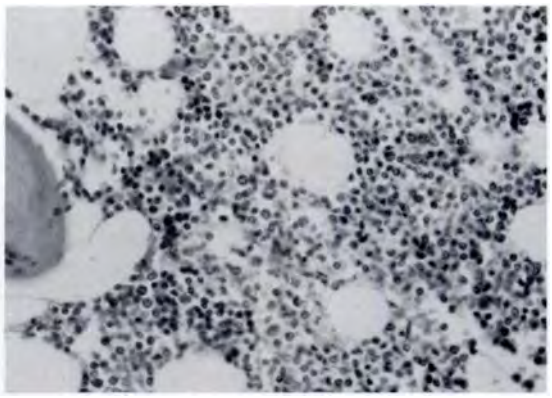

Fig. 18. Autopsy specimen of bone marrow in a patient who had received total body irradiation for 3 years and 8 months to a total of 930 r.

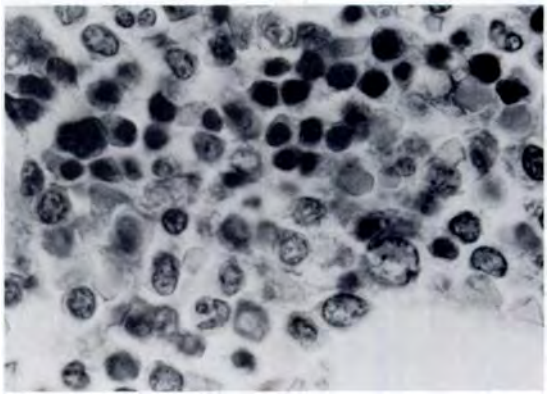

Fig. 19. Higher magnification of autopsy specimen of bone marrow in another patient who received total body irradiation for over 7 years to a total of 2,760 r.

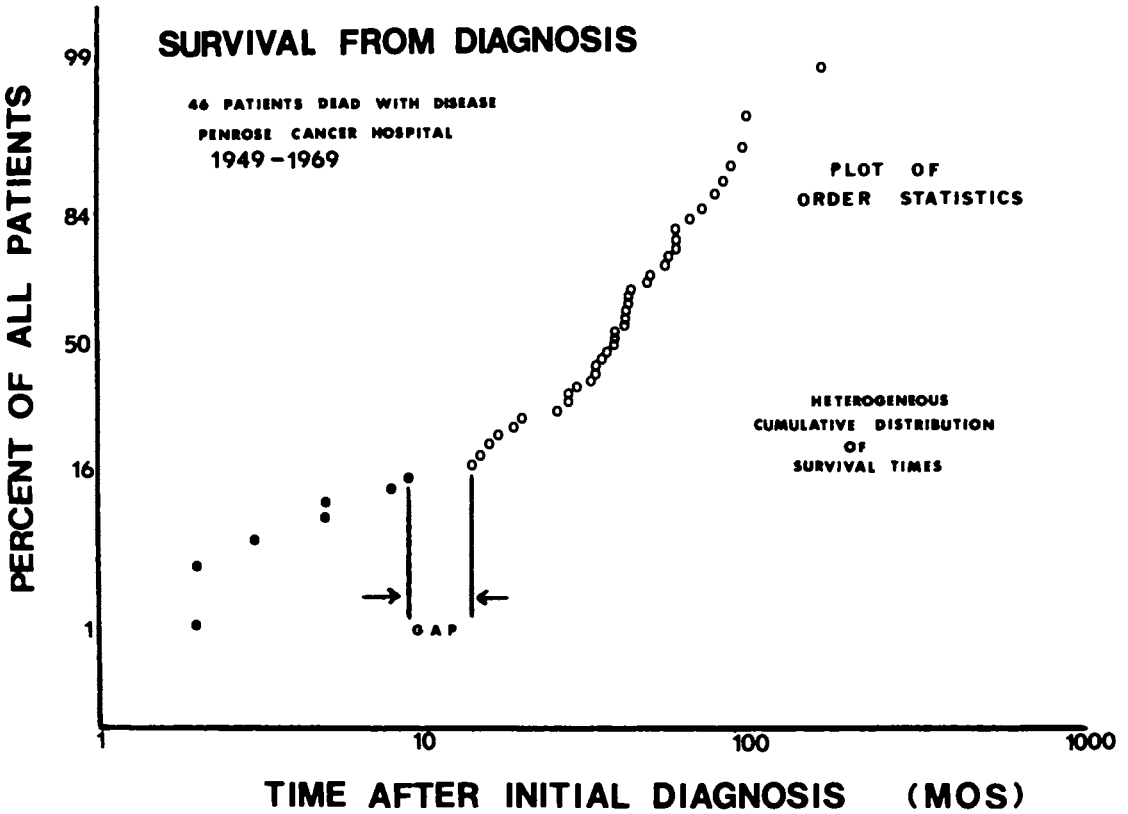

FIG. 20. Cumulative distribution of duration of survival from date of diagnosis (data of Penrose Cancer Hospital only). If the durations of survival of patients dying with leukemia are distributed log normally the shape of the cumulative distribution suggests that the corresponding frequency distribution is bimodal. The relative width of the gap permits the hypothesis of unimodality of the frequency distribution to be rejected with the probability of Type 1 error of 0.02.

tated transfusions or steroid therapy. Platelets frequently decreased in numbers, rarely to very low levels (Fig. 11). Although low platelet levels persisted in some patients, there were no bleeding tendencies apparently related to it. In only one instance of a patient with initial low platelet count, was there further decrease and some subcutaneous ecchymoses before death; the autopsy revealed massive bone marrow leukemic replacement.

The palliation afforded these patients was often immediately acknowledged. The patients seem to be comfortable until the inevitable terminal complications occur. A large proportion of these cases died of pneumonia and other infectious complications compounding the pathologic talley of their advanced age; there was one instance of cardiac tamponade due to pericardial effusion. In 20 cases an autopsy was done; the postmortem findings varied, but as a rule there was leukemic involvement of various organs in addition to multiple lymph node enlargement and splenomegaly. In most instances infiltrates were found in the kidneys (Fig. 13), liver and lungs (Fig. 14), and occasionally also in the meninges (Fig. 15), thyroid, pleura, pericardium (Fig. 16), adrenals, stomach, small and large bowel (Fig. 17), bladder, and prostate. In no instance were there signs of radiation effects or injury of the bone marrow or other structures examined; patients who had received total body irradiation for several years had rather healthy appearing bone marrows except for the present leukemic infiltrates (Fig. 18; and 19).

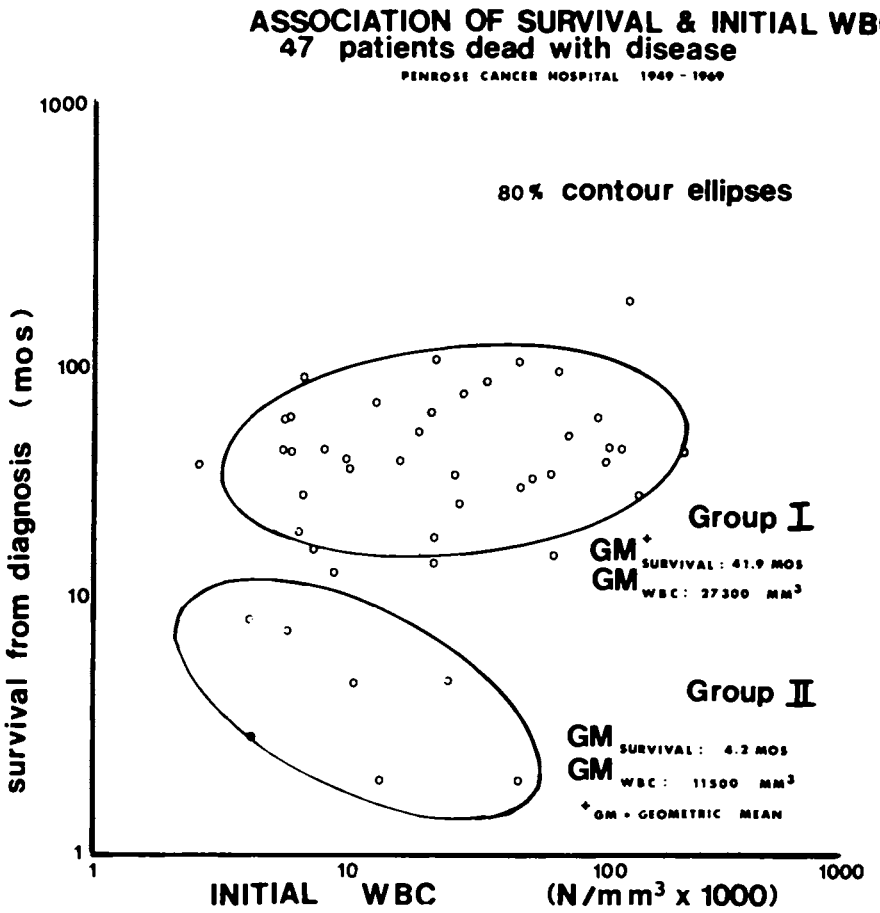

FIG. 21. Bivariate distributions of $\log_{10}$ (duration of survival from diagnosis) and $\log_{10}$ (WBC at diagnosis). (Data of Penrose Cancer Hospital only.) The pattern suggests that this bivariate distribution is heterogeneous. The hypothesis that the point-biserial correlation coefficient for WBC and the 2 survival groups is zero can be rejected with probability of Type 1 error of 0.05. (The point-biserial correlation coefficient measures the strength of the linear association between a dichotomous and a continuous variate.)

PROGNOSIS

The data presented result from a retrospective survey of clinical information gathered over a period of 25 years. The sample of selected patients is relatively small; no random alternatives were used. However exiguous, any experience of this order represents considerable painstaking effort and expense. Therefore, one is obligated to analyze thoroughly the material and to extract any plausible, however tenuous, statistical suggestion which might reveal unsuspected variations and lead to a greater understanding of the problem at hand.

If the duration of survival of all of our patients, dead with leukemia, is distributed log normally (Fig. 20), the shapes of the cumulative distribution suggest that the corresponding frequency distributions are bimodal and that the sample is heterogeneous. There appear to be 2 groups of patients in the sample judging by their response to total body irradiation and their median survival. Other univariate and bivariate analyses of the material can be adduced in support of this hypothesis (Fig. 21; and 22). It is natural to seek some empirical method of identifying, *a priori*, members of these 2 hypothetical groups. A decomposition of the bivariate distribution

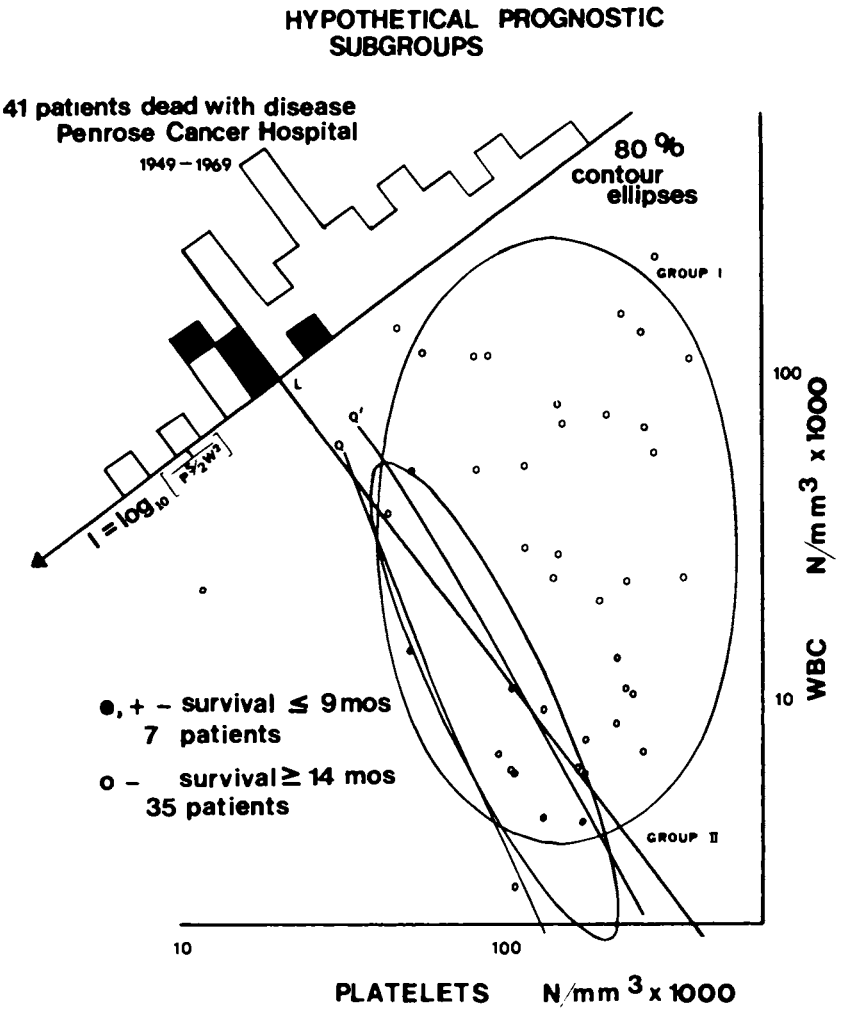

FIG. 22. Bivariate distribution of initial values of $\log_{10}$ (WBC) and $\log_{10}$ (platelet). The arrow 1 is parallel to the linear discriminant function for the 2 variates. L is the value of this linear form which best discriminates between the 2 response groups. Q, Q^1 are values of the quadratic form which best discriminates between the 2 response groups. The 2 histograms erected upon the Line 1 represent the marginal distributions of the values of the linear form in the 2 response groups. The hypothesis of homogeneity can be tested by a measure of the overlap of these marginal distributions. The hypothesis is rejected with a probability of a Type 1 error of 0.05.

of initial white blood cell and platelet counts according to survival after total body irradiation is shown in Figure 22; these 2 variates were selected on the basis of the strength of their linear association with the 2 survival groups (point-biserial correlation). Linear and quadratic forms discriminate moderately well between the 2 survival groups, but the size of the sample would not permit a realistic appraisal of the size of the possible error.

A decomposition of the distribution of survival times shown in Figure 20 is presented in Figure 23: there seem to be 2 different homogeneous groups in reference to survival.

The analysis of the survival data suggests the existence of 2 different groups of patients with chronic lymphogenous leukemia. Others have found suggestion for subgrouping in serial studies of bone marrow.

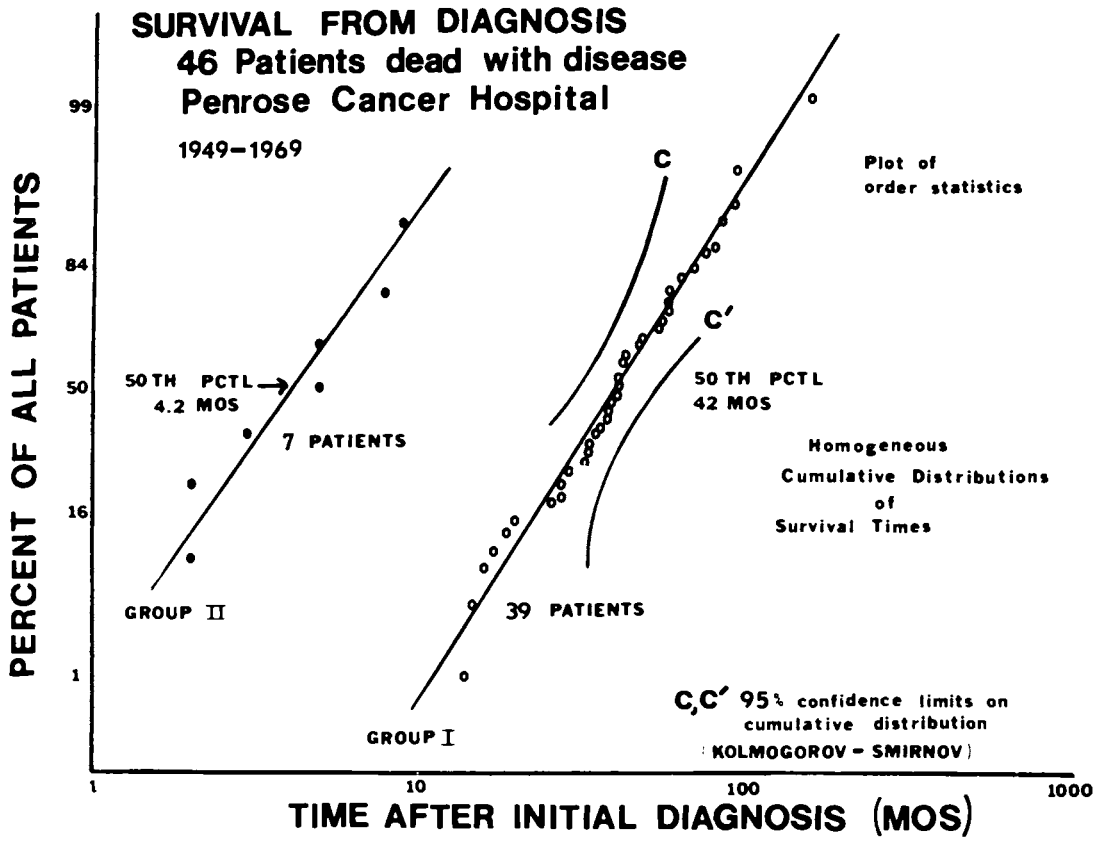

FIG. 23. Cumulative distributions of duration of survival from diagnosis for 2 groups. The heterogeneous distribution of Figure 20 has been decomposed into a superimposition of 2 homogeneous distributions.

ENVOIE

Our experience would appear to justify a more aggressive irradiation in the hope of better results. In the past we have found the margin of safety of total body irradiation to be rather narrow. Someone with a lifetime ahead might wish to explore the possibilities of larger doses again. Whereas total body irradiation seems useful, it is so primarily because it allows regional irradiation at longer intervals and with less than customary intensity. It would appear that irradiation of organs found frequently involved at autopsy, before their involvement has become manifest, may be well justified in order to allay the advent of complications and to prolong life. Thus, total body irradiation could be systematically complemented by periodical regional irradiation of kidneys, lungs, liver, as well as of spleen and lymphadenopathies; the doses necessary for these purposes may be rather moderate, permitting their being repeated at intervals.

CONCLUSIONS

1. Total body irradiation is a satisfactory procedure in the palliative treatment of chronic lymphogenous leukemia.

2. An initial series of 10 daily irradiations of 10 r may be safely followed by weekly exposures of 5 r and annual "boosters" of 100 r delivered in 10 days. Patients have been kept on this regimen for periods of 4 to 7 years.

3. In a series of 61 patients so treated the average survival was 46 months, with a maximum of 15 years, a minimum of 2 months, and a 5 year survival of 21 per cent.

4. Autopsies performed in one-third of these patients failed to reveal one instance of untoward radiation effects.

5. Total body irradiation has to be complemented by regional irradiation of spleen and lymphadenopathies. Those organs frequently found involved at autopsy such as kidneys, lungs, etc. should perhaps be similarly irradiated at very moderate doses.

6. Statistical study of the survival data suggests the presence of 2 different subgroups in the sample.

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The observations which form the basis of this lecture have been patiently gathered over the years by my faithful associates and by dozens of our residents in training: it is their work that I have presented.

For the analysis of the data and the preparation of statistical illustrations and the statistical hypothesis, I am indebted to Don Herbert, Ph.D., and for the photomicrographs, to Don Dawson, M.D., both of our staff. Richard A. Smith has been most patient and helpful in the drawing and lettering of illustrations.

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