Staff Meeting Bulletin
Hospitals of the » » »
University of Minnesota

Radiation Therapy

Volume XI Friday, May 9, 1942 Number 25

STAFF MEETING BULLETIN
HOSPITALS OF THE . . .
UNIVERSITY OF MINNESOTA

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Published for the General Staff Meeting each week during the school year, October to May, inclusive.

Financed by the Citizens Aid Society.

William A. O'Brien, M.D.

I. LAST WEEK

Date: April 26, 1940

Place: Recreation Room,
Powell Hall

Time: 12:15 to 1:35 P.M.

Program: Movie: "Invisible Clouds"

Appendicitis in College Students
L. H. Fowler
J. J. Boehrer

Discussion
C. H. Wangensteen
L. Sperling
Ruth Boynton
H. S. Diehl
W. Shepard

Present: 144

Gertrude Gunn,
Record Librarian

- - -

II. MOVIE:

Title: "The City"

Released by: Bureau of Visual Educ.,
University of Minnesota

- - -

III. ANNOUNCEMENTS

1. SPECIAL LECTURE

Monday, May 6, 8:15 p.m., Medical Sciences Amphitheatre by Dr. Reidar Sognnaes of University of Norway on "The Islands of Tristan da Cunha."
Lecture given under auspices of the Dental College. Will consist of description of health conditions of inhabitants of these islands which are located in the South Atlantic, 1300 miles from their nearest neighbors. Position is approximately midway between South America and Africa.

- - -

2. CENTER FOR CONTINUATION STUDY

Health Problems of College Students - May 2 - 4.
Electrocardiography - May 13 - 18.
Diseases of Infancy and Childhood - May 20 - 25.
Medical, Hospital, and Institutional Librarians - May 22 - 24.
Gynecologic Tumors - June 6 - 8.

- - -

3. SPECIAL SERVICE

The Mimeograph Department announces the installation of a special mimeograph photochemical printer. It will reproduce any size drawing up to $7\frac{1}{4}$" x 14" on paper not larger than $8\frac{1}{2}$" x 15". The tracings must be made on paper thin enough to be placed in the machine, as it will not take cardboard. The method will reproduce as many drawings as may be obtained from an ordinary stencil. Special prices. Tracings may also be made from any kind of India ink tracing on cloth or paper. Be sure to consult the Mimeograph Department before making the drawings to be reproduced.

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4. MINNESOTA HOSPITAL ASSOCIATION

The 17th Annual Convention of the Minnesota Hospital Association will be held May 23 - 25 at the Nicollet Hotel.

- - -

1. SURVIVAL STUDY OF ROENTGEN-RAY THERAPY IN MAMMARY CARCINOMA

An Analysis of 736 Patients Treated at the University of Minnesota Hospitals

F. R. Gratzek

Historical

As early as 1500 B.C. carcinoma of the breast was treated by excision and by a variety of escharotics, including the Egyptian arsenical pastes. Hippocrates burnt out carcinoma by cautery, the diagnosis probably being uncertain at that time, but is probably the earliest record of destruction by heat.

General Etiology

Incidence[5]:

According to Hoffman[13] the number of deaths from cancer in 1920-1929 were 146.6 per 100,000 population. The incidence rate of cancer of the breast was 54.6 for single women to 49.1 for married, widowed and divorced women. In 1935, according to the U.S. Census, cancer of the breast caused 13,226 deaths, which was 9.2% of the total cancer mortality of that year. Hoffman estimates that the patient with carcinoma of the breast lives about 4 to 5 years from the time when the cancer began to the time of death and that if 13,000 women die annually from this disease, he concludes that about five times that number, or 65,000 women in the United States are constantly suffering from cancer of the breast.

Age[10]:

Most authors report about 75% of cancer of the breast in women past the age of 40 years, although no age past adolescence seems to be immune. Brewer reports a fibroadenoma with carcinomatous areas in a negress of 16 years.

Sex[5]:

Carcinoma of the male breast is relatively infrequent. Most authors report only .5% to 3% male breast carcinoma. The University of Minnesota hospitals' incidence in this report is .41%.

Heredity:

Several authors report carcinomas of various organs as occurring in families from 5% to 24%.

Maude Slye[25] has found that selective breeding may ultimately produce strains of animals in which different organs or systems will acquire a definite predisposition to certain types of cancer.

In a study by Schreiner and Stenstrom[24], a history of cancer in the family in 122 (22%) of 563 cases of cancer of the breast, was found.

Lactation and Pregnancy[10]:

Earlier investigators[5] found that in their series of cases, carcinoma of the breast was more frequent in women who did not bear children. Ewing[10] states that pregnancy is without definite influence.

More recent[18] experimental evidence seems to indicate that in certain strains of mice spontaneous incidence of tumors of the mammary glands in breeding females a year old or over is between 80 and 90%, whereas in virgin females of the same age and strain the incidence of this type of tumor is only 50%.

Location[10]:

A slight predominance in the upper axillary segment of the left breast seems to have been established by statistical studies.

Other Etiological Factors:

In elderly individuals carcinoma of the breast is usually of a slow course, and fibrosis and cicatrization are prominent. If acute carcinosis occurs, it is usually found in women under 35 year of age with well developed breasts.

Injury may accelerate growth, and traumatism has been asserted or suspected in from 5% to 13% of patients, as a causative or predisposing factor in breast carcinoma

Injected oestrogenic substances[2] will cause growth of the male mammary rudiments to the point where fatal mammary carcino-

mas develop.

Pregnancy influences the rapid growth of pre-existing breast carcinoma in humans.

Treatment

Twenty-five years ago carcinoma of the breast was treated almost exclusively by surgery. Today radical surgery is still the method of choice generally, but evidence indicating the value of radiotherapy is accumulating very rapidly so that it is commonly employed as a supplementary procedure.

The use of x-rays in the treatment of cancer of the breast began in 1914 with the advent of the Coolidge tube, although as early as 1896, Emil Grubbe of Chicago treated a patient with cancer of the breast with x-radiation.

Technics and methods of treatment have changed from year to year, and vary in many clinics today, so that to estimate the results of treatment on a statistical basis is extremely difficult[21,28], and data concluded upon, for those reasons, are open to criticism.

Combined operation and irradiation is the method of treatment advocated by the majority of radiologists and postulates thorough radical mastectomy followed by irradiation adequate to destroy all cancer cells in the bed of the tumor and surrounding tissues.

Radical[17] operations have become quite standardized by skilled and experienced surgeons. In them, the mammary gland, fascia, muscles, and axillary contents are removed "en masse." But unfortunately cancer of the breast is not confined within these limitations as is evidenced by the fact that the general average of surgical curability, on the basis of the five year survival rate is approximately thirty percent. This means that in seventy percent of the cases the disease had extended beyond the possibility of removal by the time operations were performed.

The only modern method of treatment known to be effective in cancer of the breast is surgery, either followed or preceded by roentgen-ray irradiation with addition of radium or radon where indicated in selected cases.

Pre-operative irradiation is being used and advocated by several well known clinics on the basis that the most highly malignant cells will be destroyed or attenuated in their growth and spread. The objection to this procedure is the necessity of a biopsy in most instances for a definite diagnosis, therefore opening a possible channel for spread due to surgical manipulation.

Because of the frequency of recurrences in all forms of malignancy regardless of response to surgery, irradiation, or their combination, it is recommended that every patient with carcinoma of the breast be under observation for many years and be carefully examined at stated intervals after treatment.[4]

Theoretical and Biological Considerations for Postoperative Roentgen-Ray Therapy

Local postoperative treatment is intended: (1) to destroy any malignant cells that may have been transplanted during operation; and (2) to destroy any microscopic remnant of cancerous tissue in the area treated which the surgeon may have missed. Definite evidence of implantation is furnished by the rare observance of stitch hole recurrences. Other more frequent implantations probably occur under the skin flap.

To get the best effect the postoperative treatment should be started as soon as the patient's general condition and circumstances will permit, usually 10 days to 2 weeks after operation, even though the wound is not entirely healed. Postoperative irradiation, if mild, does not interfere with the healing of the wound, but the healing period may be prolonged if the doses are large.

It is well known that cancer of the

breast is more malignant in young women, also, it grows more rapidly during pregnancy. Experiments indicate that the ovarian hormones stimulate the production of cancer of the mammary glands in animals that have any susceptibility to the disease. On these facts, it is recommended by many investigators, that all women who have carcinoma of the breast and are still in the menstrual age, should be given an ovarian sterilization of deep roentgen-ray therapy.

Analysis of University of Minnesota Hospitals Cases

In the analysis of all cases of carcinoma of the breast referred for deep roentgen-ray therapy at the University of Minnesota Hospitals from July, 1926 through December, 1938, 736 patients were treated. In this analysis we chose the date of the first deep roentgen-ray treatment as the beginning of our survival period, although most of these patients had either surgery, radon implantation or other forms of treatment preceding roentgen-ray therapy.

We have been able to follow all except 18 patients (2.4%) up to December, 1938, or to expiration by the systems of:

1. Personal examination.
2. Tumor Clinic examination.
3. Questionnaire mailed to the patient or a relative.
4. Telephone contact with the patient, a relative, or friend in the Twin Cities.
5. Questionnaire mailed to the patient's local physician.
6. Investigation of death records in the State Bureau of Vital Statistics.

Some of the 18 unknown patients have been followed up to 6 years and then lost track of, and these have been deducted at that time from our final survey, a few of these were not seen or heard from following the completion of therapy, and have been excluded in this report as survivors, but are included in the total number treated.

Because of insufficient evidence on our records or insufficient information from surgeons referring the patients from elsewhere, it was impossible to make any definite pathological classification based on the grade system which is so widely used in recent years. Furthermore, because of the great number of patients referred from surgeons outside of the University Hospitals Staff, it was difficult to ascertain the exact type and stage of each case. It, therefore, became necessary to group the patients into three classes as carcinoma of the breast:

1. Those referred for postoperative prophylactic therapy, where the axillary nodes were supposedly involved and a radical mastectomy preceded therapy only within a reasonable recent enough period so that recurrences or metastases were not evident. It is possible that in this group patients may have been referred for irradiation by surgeons, where no axillary nodes were involved, and no microscopic study was made of the nodes to verify or deny carcinomatous metastases.

2. Those with recurrences or metastases who had either a simple palliative mastectomy or had a radical mastectomy. In some of these patients, distant metastases were present but not evident, previous to the operation.

3. Those inoperable cases where there was very massive breast involvement, distant metastases were present on first examination, or that the age or physical condition of the patient was such that the operative risk was poor.

Number treated: 736 patients were treated by roentgen-ray therapy.

Sex: 733 females and 3 males.

Age: Patients were divided into age groups in one-half decades so as to show definitely the very pronounced increase in the incidence of carcinoma of the breast after the age of 35 years. We find in our series that 87% of the

patients were between the ages of 35 and 70 years, and 85% are past the age of 40 years. Our youngest patients were 22 years of age, and the oldest 91 years of age.

Table No. I

Age Group Divided in One-Half Decades
699 Patients

Age	Cases	Percent
20-24	5	.7%
25-29	9	1.0%
30-34	28	4.0%
35-39	62	9.0%
40-44	92	13.0%
45-49	109	15.0%
50-54	111	17.0%
55-59	90	13.0%
60-64	69	10.0%
65-69	72	10.0%
70-74	28	4.0%
75-79	13	2.0%
80-84	10	1.0%
85-89	0	0.0%
90-94	1	.1%

These figures show quite definitely that our patients fall into the higher age groups, as compared to others; i.e., past the age of 40 years (85%), as most authors report 75% of their patients above the age of 40 years. Lewis[16], of Johns Hopkins Hospital, found 81% in a series of 950 patients to be over 40 years of age and Nathanson[19] reports a peak incidence in a series of 2165 patients to be in the 46 to 48 year age group.

Symptoms and Duration

Out of the 736 patients treated, 686 gave definite histories of symptoms such as mass, pain, ulceration of the breast, discharge from the nipple, etc. 100 patients (15%) had symptoms of one month or less, and 457 patients (66%) with admitted symptoms of one year or less, the remaining 229 patients (34%) had symptoms over one year.

Table No. II

Duration of Symptoms

Duration	Number	Percent
1 mo. or less	100	15%
2-4 mos.	148	21%
5-7 mos.	95	14%
8-12 mos.	114	17%
Over 1 year	229	34%

The shortest admitted duration of symptoms in the patients was 2 weeks before roentgen-ray therapy and only 3 days before surgery was performed. The longest duration of symptoms was 42 years (1890 to 1932) in which patient we wish to present a resumé of the record. This patient was a married female, age 68 years, who gave a history of having noticed a bean sized mass in the medial side of her left breast since 1890. She was caring for her invalid mother, and in moving her in bed frequently caused considerable pressure of the left breast while adjusting the invalid. In December 1931, she noticed a pain in the left breast, and on January 8, 1932, had a left radical mastectomy at another hospital, and a round mass 2 cm. in diameter was found to be a carcinoma. This patient was referred to the University Hospitals for roentgen-ray therapy on April 26, 1932, at which time examination revealed cervical, supraclavicular, and right axillary palpable nodes. Microscopic report of a cervical node biopsy was "undifferentiated carcinomatous metastases." From September 7, 1932 through September 14, 1932, she was given 1,000 r (measured in air) deep roentgen-ray therapy to the left breast region and 250 r added to the right axillary and left supraclavicular and cervical regions On January 10, 1933, she was last seen in the Tumor Clinic and had metastases to the left humerus in addition to other regions. She expired on 4/5/33. This is a case of a benign breast tumor of many years standing with a late malignant degeneration.

Classification of Patients

Table No. III

Classification of Patients in Groups According to Years and Number of Patients Referred for Treatment

Year	Postoperative Prophylactic	Metastatic and Recurrent	Inoperable	Total
1926	2	13	2	17
1927	13	19	2	34
1928	9	12	2	23
1929	22	17	1	40
1930	18	28	4	50
1931	28	31	9	68
1932	30	33	12	75
1933	36	47	7	90
1934	19	46	12	77
1935	22	32	16	70
1936	13	22	12	47
1937	25	20	16	61
1938	18	52	14	84
TOTAL:	255 (35%)	372(50%)	109(15%)	736

From the above table, it is evident that 255 patients (35%) were referred for postoperative prophylactic deep roentgen-ray therapy; 372 patients (50%) as recurrent and metastatic and 109 patients (15%) as inoperable.

Postoperative Prophylactic Group

From the following table which includes 237 (36.5%) patients out of 652 treated as postoperative prophylactic cases from July, 1926, through December, 1937, we can see the survival from one to 12 years. In our report we eliminate the 84 patients treated during the year of 1938 as enough time had not elapsed to qualify these patients in our yearly survival data.

Table No. IV

Percent Survival of Patients Treated as Postoperative Prophylactic Cases

Years	Number Treated	Number Surviving	Percent Surviving
1	237	204	86%
2	212	153	72%
3	199	128	64%
4	177	102	58%
5	158	76	48%
6	122	50	41%
7	92	30	33%
8	64	19	30%
9	46	12	26%
10	24	10	
11	15	6	
12	2	1	

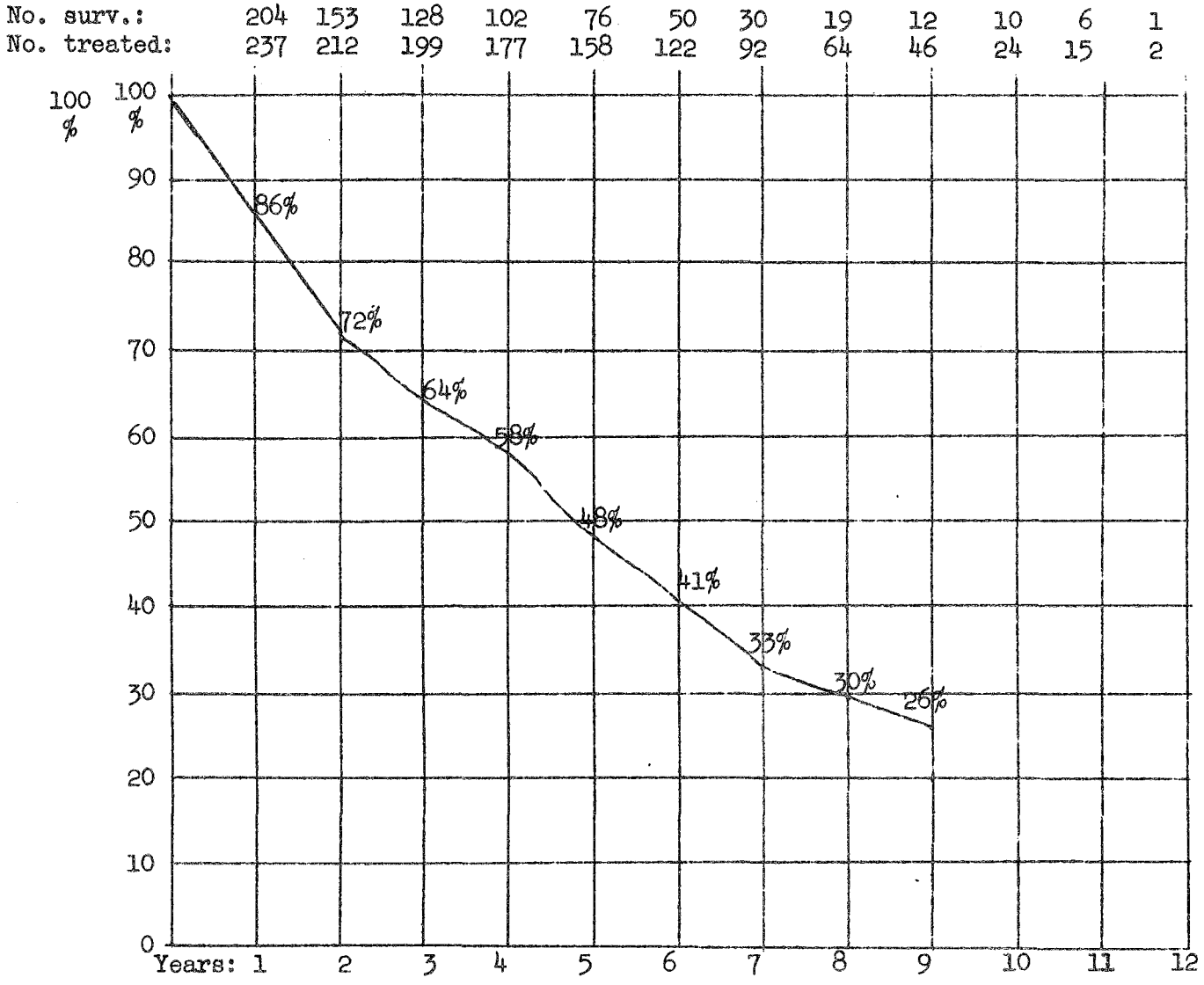
We see that there were 199 patients treated as postoperative prophylactic cases with a 3 year survival of 128 patients or 64% and in the same group we find that 158 patients were treated, and 76 (48%) survive a 5 year period.

Graph No. I exemplifies the survival curve in this group.

Graph No. I

Survival in Group with Carcinoma of the Breast Treated by Irradiation Therapy Immediately Following Radical Mastectomy

University of Minnesota Hospitals, July 1926 through December 1937



These figures, when compared with reports of authors from various clinics, indicate that our results of treatment, in the stage II carcinoma of the breast, are quite closely comparable with others. The following table taken from Pfahlers[21] publication of 1938, shows the comparative results in 5 year survival in stage II carcinoma of the breast from surgery alone and surgery and irradiation combined.

Recent Comparative Statistics from the Same Clinics

AUTHOR	Operation Alone, Percentage Living 5 years			Operation and Irradiation, Percentage Living 5 years		
	No. of Patients	Stage 2	All Patients Operated On	No. of Patients	Stage 2	All Patients Operated On
Siemens, W.: Strahlentherapie 47:627 (Aug.9) 1933.....	104	33.6	....	188	53.2	....
Harrington*.....	604	24.3	....	1447	28.8	....
Gentil, Franicisco, and Guedes Bernard: Arq.d.pat.2:122,1928	42	20.6	....	83	42.5	....
Adair.....	...	20.6	35.0	...	23.0	40.6
Hintze.....	656	....	30.5	183	....	53.0
Portmann.....	85	....	35.6	99	....	46.0
Ganz,Ernst: Strahlentherapie.. 57:413-414, 1936.....	3599	....	31.2	118	....	40.0

*Operations were done at the Mayo Clinic, but postoperative irradiation mostly by radiologists throughout the country. The irradiation, therefore, is not likely to have been on as high a plane as the operation. (Courtesy, J.A.M.A., Feb. 19, 1938.)"

Adair reports a 5 year survival of 41%; Hintze, 53%; Portmann, 46%; and Ganz, 40% as compared to our 48% in a similar group of patients. It might be possible that our results would be a great deal better if in the survival of patients the actual cause of death was considered and those patients who have died from other causes besides recurrent and metastatic breast carcinomas eliminated because, as previously stated in our age grouping, 85% of our patients were past the age of 40 years as compared to 75% of most other authors, therefore, the usual life expectancy in our series should naturally be less even if carcinoma were not present. Evans and Lecutia[9] in a recent report found that in their series 50% of the patients treated by surgery and roentgen-ray therapy in Stage II carcinoma of the breast survived 5 years and 42% survived 10 years as compared to our 48% five year and 41% ten year survivals. Wintz[27] in his 1935 report on Stage I and II carcinomas of the breast shows a 68% three year survival based on 136 patients treated, 48% five year survival based on 124 patients treated, and a 32% ten year survival based on 77 patients treated.

Recurrent, Metastatic and Inoperable Groups:

It is not the purpose of any radiologist to claim a high percentage of cures in those unfortunate individuals who have postoperative carcinomatous recurrences, bone or other metastases, or are inoperable, but it is known that many extremely painful metastases have responded so well to roentgen ray therapy that bedridden patients were able to resume their duties in their home for many months with freedom from pain or other discomfort, inoperable patients have been made operable following therapy, and recurrences have subsided satisfactorily.[20]

The following table includes 415 patients (64%) out of the 652 treated as recurrent, metastatic, or inoperable patients, of which 243 (59%) out of the 415 treated survived one year; 86 patients (25%) out of the 345 treated survived 3 years; and 29 patients (12%) out of the 239 treated survived 5 years.

Table No. V

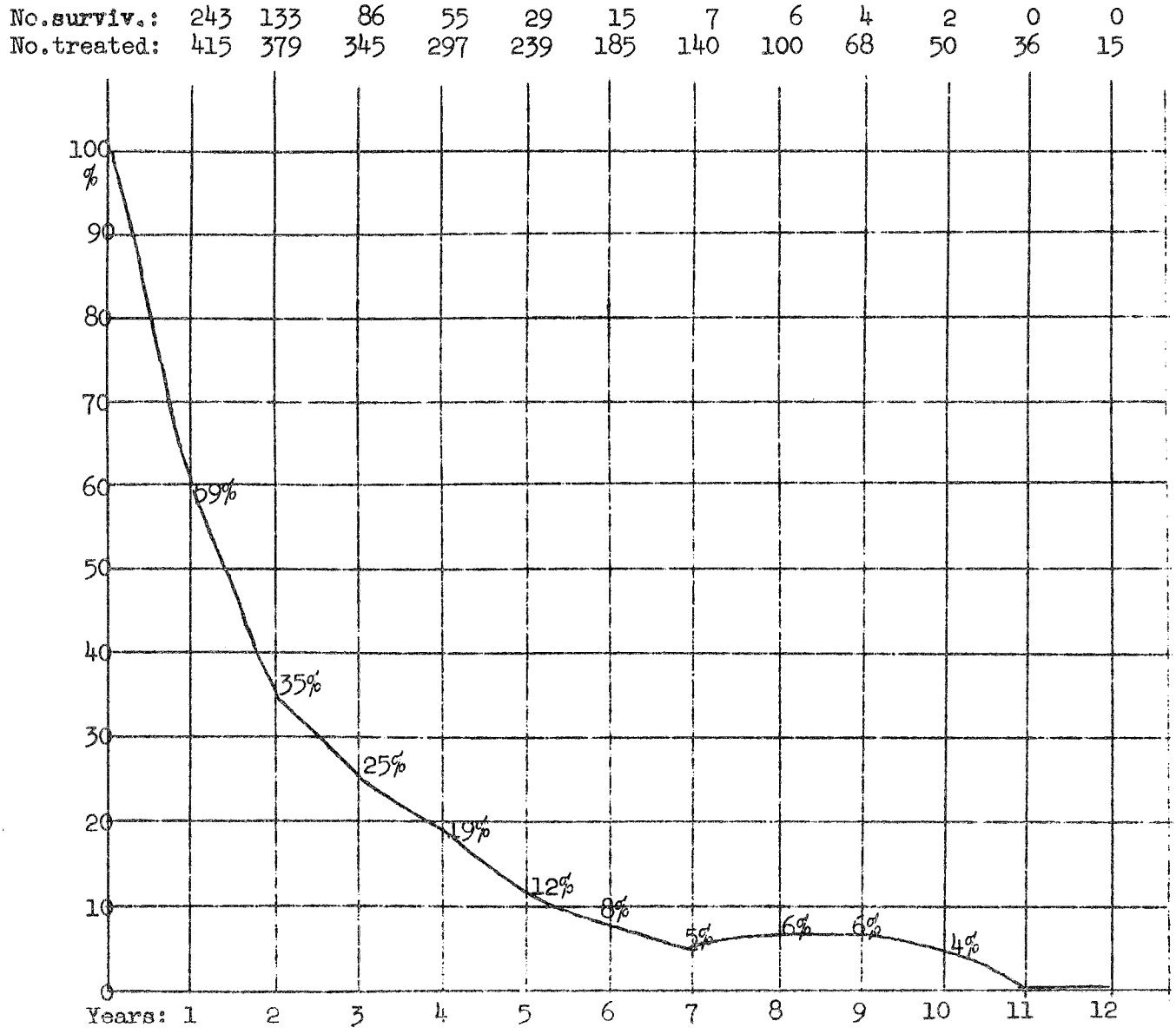
Percent Survival of Patients Treated with Recurrences, Metastases, or Inoperable Carcinomas

Years	No. Treated	No. Surviving	% Survival
1	415	243	59%
2	379	133	35%
3	345	86	25%
4	297	55	19%
5	239	29	12%
6	185	15	8%
7	140	7	5%
8	100	6	6%
9	68	4	6%
10	50	2	4%
11	36	0	0%
12	15	0	0%

The following graph indicates the survival curve in this same group.

Graph No. 2

Survival in Group with Recurrent, Metastatic, and Inoperable Carcinoma of the Breast Treated by Irradiation and Other Forms of Therapy. July 1926 thru December 1937. (Survival from date of first roentgen-ray treatment.)



It is obvious that the number surviving over 7 years is too small to have much statistical value. The patients in this group who survived up to 10 years were probably cases where there might have been a mistake in diagnosis as regards metastases, or possibly definite cures as the following case may exemplify.

This patient was a single female, age 45 years, referred to the University Hospitals on December 22, 1933. She gave a history of having noticed 3 lumps in her right breast and one in her left breast since 1908 (25 years). She was seen in the University Hospitals Out-Patient Clinic in 1913 (5 years after

onset), but because of the multiplicity of the nodules, she was advised to leave them alone as the condition was considered benign. No biopsy was taken. About October, 1933 (20 years following her first examination) the patient noticed a new "string of lumps" located medially in her right breast and on December 7, 1933 she consulted a private physician, who immediately referred her to the University Hospitals. Physical examination revealed multiple masses in her right breast with right axillary and right supraclavicular palpable nodes. One mass was present in the medial side of the left breast and a palpable node was present in the left axilla. A few of the masses in the right breast were attached to the skin and some of these were excised by diathermy on December 23, 1933 and a microscopic study revealed scirrhous carcinoma. December 28, 1933, 49.3 m.c. of radon implants (6720 m.c. hours) were inserted into the right breast, right axilla, and right supraclavicular regions. During May 1934 she received 100 r (measured in air) deep roentgen-ray therapy to her right breast and 200 r were added to the right axilla and right supraclavicular areas. She was followed in the Out-Patient Tumor Clinic up to June 1937, and on November 2, 1938 she reported by telephone that she was feeling fine and had no recurrence. In this patient it is probable that she had a benign lesion in the left breast with an inflammatory adenopathy in the left axilla, as these areas have remained dormant without any type of therapy. This patient survived 5 years without recurrence where no radical surgery was performed and irradiation and radon implantation were the main forms of therapy given.

Subdividing the above patients into those with recurrences and metastases and those who were inoperable we find that:-

1. 372 patients (50%) of the entire group of 736 were treated as recurrent and metastatic carcinomas of the breast, and out of this group 320 were treated from July, 1926 through December, 1937. The following table shows the per cent survival.

Table No. VI

Percent Survival of Patients with Recurrent and Metastatic Carcinoma of the Breast
(July 1926 - December 1937)

Yrs.	No. Treated	No. Surviving	% Survival
1	320	196	61%
2	300	115	38%
3	278	71	26%
4	246	44	18%
5	200	26	13%
6	153	13	8%
7	120	5	4%
8	89	5	6%
9	61	4	6%
10	44	2	5%
11	32	0	0%
12	11	0	0%

We notice a 3 year survival of 71 (26%) out of 278 patients treated, and 26 (13%) out of 200 patients treated surviving 5 years.

2. In the patients considered to be inoperable we find that out of the 109 cases referred for therapy, 95 were treated up to December, 1937. As was previously explained, these patients were considered inoperable because of either acute carcinomatous involvment, very extensive local lesion and metastases, or because of being poor surgical risks. The following table shows that 47 patients of the 95 treated (50%) survived one year, 15 out of 67 patients treated (22%) survived 3 years, and 3 patients out of 39 treated (8%) survived 5 years.

Table No. VII

Percent Survival of Patients with Primary Inoperable Carcinoma of the Breast

Years	No. Treated	No. Surviving	% Survival
1	95	47	50%
2	79	18	23%
3	67	15	22%
4	51	11	21%
5	39	3	8%
6	32	2	6%
7	20	2	
8	11	1	
9	7	0	
10	6	0	
11	4	0	
12	4	0	

Many of the patients became operable after an intense series of roentgen-ray therapy, but others have had only radon implantation and deep roentgen-ray therapy, and have survived for several years.

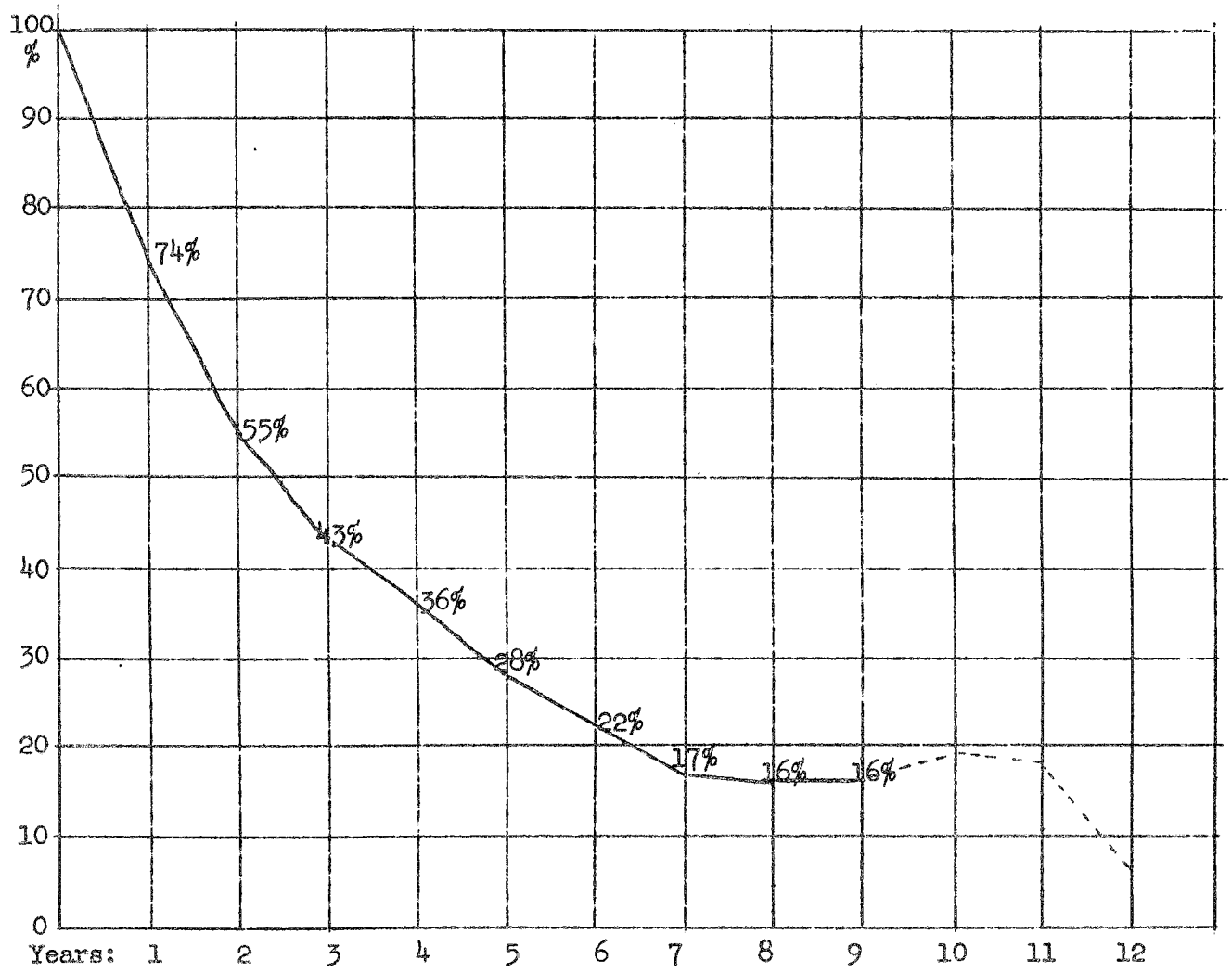
Survival of Entire Group:

In a study of the entire group of patients treated by deep roentgen-ray therapy either alone or following all operative procedures we find the following graph to represent our survival curve.

Graph No. 3

Survival in All Clinical Groups with Carcinoma of the Breast Treated by Irradiation and Other Forms of Therapy. (July 1926 - December 1937)

No. Surviv.:	481	322	235	171	111	68	39	27	18	14	9	1
No. Treated:	652	591	544	474	397	307	232	164	114	74	51	17



It is noticeable that in the survival here, when no consideration as to the stage of the disease is given, we have a 28% five year survival based on a total number of 397 patients treated and a 10 year survival of 19% based on a total of 74 patients treated. These figures compare with those of Evans and Lecutia[9] very closely; their 5 year survivals being based on 830 cases treated with a 30% survival, and a 10 year survival of 22% based on 434 cases. In Lewis' and Rienhoff's[16] report of 1931 it appears that about 23% of their combined medullary, scirrhous, and adenocarcinomas survived 5 years.

Metastases and Recurrences: In the entire group of patients where metastases are specified in the records, we find that the axillary and supraclavicular nodes, bones, and lungs predominate as the sites of metastases. Bell[6] states that over two thirds of the cases show axillary metastases at the time of operation while Trimble[26] states that in 80% of the patients presenting themselves for examination because of a lump in the breast metastases have already occurred. Lewis and Rienhoff[16] substantiate our observations in finding that usually the younger the patient with carcinoma of the

breast, the more susceptible she is to local or axillary recurrences.

The following table shows the incidence of metastases in each region and local or axillary recurrences. Under the column headed as "other regions" in this table are included such metastatic sites os the omentum, intestines, peritoneum, genito-urinary system, inguinal nodes, etc., and often instances specified in the records as "generalized metastases." These figures include metastases to more than one region in the same patient where it is mentioned in the record.

Table No. VIII

Region of Metastases from Carcinoma of the Breast (July, 1926-December, 1938)

Site	Numerical Incidence
Local Recurrence	54
Axillae (Recurrence)	225
Supraclavicular	78
Other Breast	20
Lung	77
Bone	148
Skin	41
Liver	25
Brain	11
Adrenal	1
Other Regions	127

You will notice that in one instance we had metastases to the adrenals, and we wish to present this unusual case in this report.

This 69 year old white female was admitted to the University Hospitals on December 1923, complaining of pain, swelling, and blue discoloration in her left breast, which occurred after she fell and injured her breast November 23, 1923, and a mass in the upper outer left breast developed. Examination revealed a mass about 4 cm. in diameter and palpable left axillary nodes. A radical left mastectomy was done on 12/5/23, and a microscopic diagnosis of scirrhous carcinoma with axillary node metastases was made. She made an uneventful recovery and was discharged. X-ray examination of the chest was negative. On 2/21/27 (3 years later) patient was readmitted, complaining of a lump in her left axilla which she had first noticed 2 weeks previously. She also had a brownish discoloration of her face, neck, and hands which had gradually been increasing since February 1, 1927, and a small ulcer on her right forearm which wouldn't heal. X-ray examinations of her gastro-intestinal tract were negative. A diagnosis of one staff physician was acanthosis nigricans and a dermatological consultant diagnosed the condition as pseudopellagra, a condition occasionally present in malignancies. She was given 4 deep roentgen ray therapy treatments amounting to 800 r (measured in air) as the total dose to the left breast region and 1,000 r added to the left axillary region. The patient grew worse and expired on March 20, 1927 on the 27th hospital day.

Autopsy findings revealed:

1. Marked yellowish brown pigmentation of the skin, more intense on the exposed regions with scaling and thickening in those parts, and a dark brown blotchy pigmentation of the mucous membranes of the mouth.

2. Large mass of tumor tissue in the left axilla.

3. Lungs, liver, spleen, myocardium, stomach, intestines and right kidney were normal.

4. Both adrenals entirely, and the upper pole of the left kidney were replaced by metastatic scirrhous carcinoma.

This is a case of Addison's disease due to bilateral metastatic carcinoma of the adrenals with no other organs involved.

Bilateral Breast Carcinoma: In the analysis of the patients with carcinoma of the breast in our series, 20 patients (2.7%) were found to have bilateral breast carcinoma either on first examination or as a secondary metastases at a later date. Some authors[16] report up to 5% of their patients with bilateral breast carcinoma, but in most instances

only 1.5% of bilateral primary involvement. Table No. IX indicates the survival of these patients from the time of irradiation to the primary tumor or following the recurrence of the carcinoma in the opposite breast which was treated surgically and was followed by irradiation therapy. The patients who had a bilateral carcinomatous breast involvement at the time of the first examination, survived only a comparatively short period, but those who had involvement of the remaining breast at some later time frequently survived several years. Lewis[16] reports the average length of life in bilateral breast carcinoma to be 5.69 years.

Table No. IX

Survival of Patients with Bilateral Carcinoma of the Breast

Years	No. Treated	No. Surviving
1	20	12
2	18	5
3	17	3
4	15	2
5	13	2
6	10	1
7	8	1
8	7	1
9	4	1
10	3	1
11	2	1

Cures are possible in this group as is exemplified by the following case:

This patient was a 41 year old married female who was first admitted to the University Hospitals in January, 1930 with a history of having noticed a mass in her left breast since 1912, which was biopsied at that time and found to be benign. In November, 1929 (17 years later), a sudden pain and swelling was noticed in the old biopsy scar. January 7, 1930 a radical mastectomy was performed and a pathological microscopic diagnosis of adenocarcinoma was recorded. Axillary nodes were reported not involved. She was referred for roentgen-ray therapy in February 1930 and 2075 r (measured in air) were given to the left breast, left axilla and left supraclavicular regions over a 12 day period. Patient had no recurrence and no metastases up to May, 1932 ($2\frac{1}{2}$ years after the primary left breast lesion), when a mass was discovered in her right breast and a radical right mastectomy was performed on May 26, 1932. A pathological diagnosis of carcinoma was made but no record was made as to whether any nodes were involved. In June, 1932, she was referred for deep x-ray therapy and was given 1000 r (measured in air) to the right breast region with 400 r added to the axilla and supraclavicular regions and a similar series was given in August, 1932. This patient was alive and well up to December, 1938, having survived a nine and seven year period respectively from carcinoma of the breasts.

Early Diagnosed Group: Since the onset of scientific therapy in all diseases, early diagnosis and treatment have been advocated and have proved to be the greatest boon to good results. In our analysis as to duration of symptoms before therapy was instituted, we found 100 patients whose symptoms were of one month or less. In this group we found 3 acute carcinomas which were inoperable cases and where therapy was of very little benefit. The remaining 97 patients had radical mastectomies followed by irradiation therapy. In 45 patients who could be followed one year or more in our series, immediate postoperative prophylactic therapy followed the mastectomies.

Table No. X

Percent Survival of Patients with Carcinoma of the Breast, Symptoms of One Month or Less, Surgery Followed by Prophylactic Deep Roentgen Therapy

Years	No. Treated	No. Surviving	% Survival
1	45	43	96%
2	37	31	84%
3	33	24	73%
4	31	24	77%
5	29	18	62%
6	19	10	52%
7	14	7	50%
8	12	6	50%
9	6	2	33%
10	2	1	

It is gratifying, therefore, to show that in this group 43 patients out of 45 treated (96%) survived one year; 24 patients out of 33 treated (73%) survived 3 years; and 18 patients out of 29 treated (62%) survived 5 years. One patient treated in the original group in 1926 is alive and well today. Two of these patients were lost track of immediately after therapy was completed.

However, 40 of these patients who had operations, but no postoperative prophylactic therapy given, were later referred as recurrent and metastatic cases. The following table shows a comparative study of the percent survival from the time of surgery and from the time of irradiation therapy.

Table No. XI

Percent Survival of Patients with Carcinoma of the Breast, Symptoms of one month or less. Treated as Recurrent and Metastatic Cases. Surgical and Irradiation Survival

Years	No. Operated	No. Surviving	% Surg. Survival	No. Irradiated	No. Surviving	% Irrad. Survival
1	40	37	92%	40	26	65%
2	38	29	76%	38	17	45%
3	36	22	61%	32	9	28%
4	32	11	34%	27	4	15%
5	28	8	28%	22	2	9%
6	23	2	9%	19	1	5%
7	21	1	4%	)		
8	20	1	5%	)		
9	15	1	7%	) None		
10	5	1	11%	)		

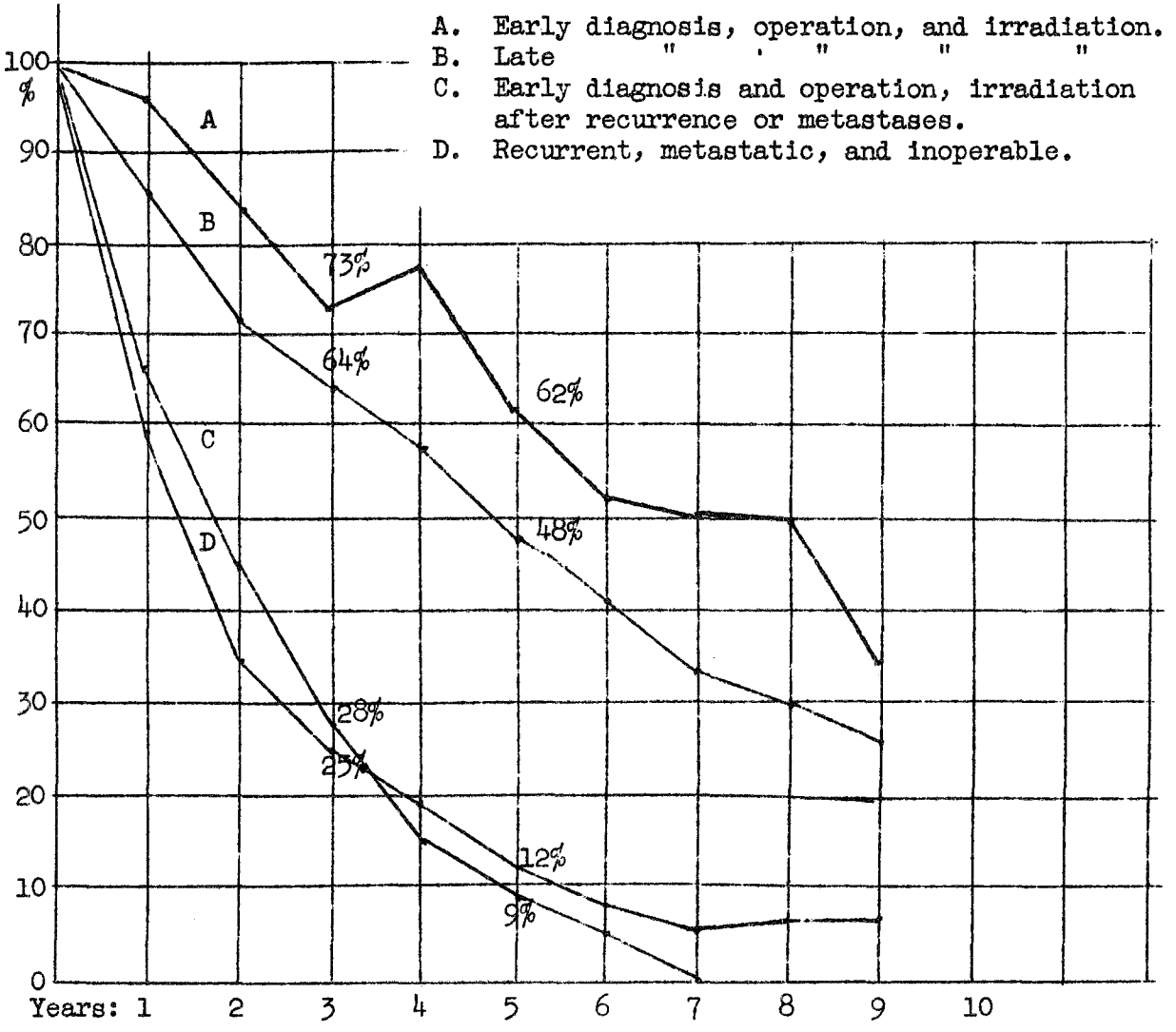
This table indicates that the irradiation survival was only 28% in 3 years and 9% in 5 years. Although the surgical survival is considerably higher, the entire group were found to have recurrences or metastases either within a few months or up to 4 years following surgery. Irradiation therapy in this group consisted of palliation in most instances as the metastases and recurrences were usually of a very malignant and widespread type so that curative therapy was impossible.

Some investigators[14,16] have found that, in instances where patients have sought medical care very early after noticing an abnormal growth or ulceration, the condition was very frequently of an acute nature and progressed rapidly. For that reason, the individual became alarmed early and requested aid, but in these same instances the malignancy was of such an acute type that even the best and most thorough treatment was of little or no benefit.

The following graph shows the comparative survival rate of four clinical groups.

Graph No. 4

Survival in Four Clinical Groups with Carcinoma of the Breast Treated by Irradiation and Other Forms of Therapy. July 1926 thru December 1937. (Survival from date of first roentgen-ray treatment.)



In the A and C curves we have the selected groups of patients which were mentioned in Tables X and XI respectively, yet the survival curve of A and B is comparable in every respect except from the standpoint of duration of symptoms before radical mastectomy and deep roentgen-ray therapy. It is, therefore, noteworthy that our three year survival in the group treated early is 73% as compared to 64% for all the patients given deep roentgen-ray therapy immediately after radical mastectomy. (See Table No. IV).

Curves C and D are compared on the basis of late roentgen-ray therapy in an early diagnosed and operated group (C), and the entire group of patients (D) referred for therapy after recurrences and metastases had occurred post-operatively, or which had progressed beyond the point of any surgical intervention. It is noteworthy here that the survival in the early diagnosed group is less beyond the third year, therefore indicating the acuteness of many of these malignancies.

Therapy Technique of Carcinoma of Breast

1. Postoperative prophylactic.

In this group the following factors are used, and it is advisable to begin therapy as soon as conditions warrant it following surgery. (10 days to 2 weeks postoperative.) 200 K.V.P. therapy unit; 30 ma current intensity 1 mm. Al. and 1/4 mm. Cu filter (H.V.L. 0.6 mm. Cu) to the anterior breast region at a F.S.D. of 70 cm. to a field including the anterior supraclavicular and axillary regions and the parasternal line medially, giving 200 r (measured in air) per treatment, 6 treatments being given over 14 days, 1200 r (measured in air) as a total dose. The output being 47.6 r per minute.

At each time a supraclavicular or axillary field is added following the treatment to the breast region. In these instances the posterior supraclavicular and posterior axillary fields are given 300 r (measured in air) per treatment at a F.S.D. of 60 cm. and a 1 mm. Al + $\frac{1}{2}$ mm Cu filter used (H.V.L. 0.9 mm Cu) and 46.4 r per minute being the output, 600 r being the total dose, and with the same factors, the anterior axilla and anterior supraclavicular regions are given 200 r (measured in air) additional. Powdered rice in small bags is used along axillary, and other skin folds, to make these areas more homogeneous when being treated.

All women in the menstrual period of life are urged to have permanent sterilization doses of deep roentgen-ray therapy to their ovaries and are required to sign sterilization permission before this is given.

2. Recurrent and metastatic technique.

In these patients every case has to be individualized from the standpoint of therapy, and it is mostly a matter of personal judgment on the part of the roentgen therapist to ascertain the amount of therapy indicated.

3. Inoperable patients.

In this group of patients the breast involved is treated in quadrants with the therapy beam directed tangentially through the breast. The breast is divided into a superior, inferior, medial, and lateral triangular quadrant, and the patient placed in such a position so as to avoid the irradiation beam striking the lung parenchyma. In the upper quadrant is included the anterior supraclavicular region, and in the lateral quadrant the axilla. Each field is treated by a fractional dose method so that at the conclusion of treatment between 1000 r to 1500 r (measured in air) has been the total dose per field, with 200 r to 300 r (measured in air) as the maximum daily dose to one quadrant. The posterior axilla and posterior supraclavicular areas are supplemented with 600 r each as a total dose.

The factors used are a 200 K.V.P. therapy unit; 30 ma current intensity, 60 cm. F.S.D. 1 mm Al and $\frac{1}{2}$ mm. Cu (H.V.L. 0.9 mm. Cu) as filters, with 46.4 r per minute as the output.

Where indicated a permanent sterilization dose of therapy is urged in each patient.

Complications and Sequelae: Occasionally patients complain of irradiation sickness just as one finds in almost any deep roentgen ray therapy treatment. This usually has no great significance, but if severe, the usual dosage is diminished until the patient's condition is improved. Some of the late sequelae are lung fibrosis as a result of irradiation penetrating the pleura and lung parenchyma and causing a pleuropulmonitis, as described by Desjardins in 1926. Skin reactions occur rarely, but usually subside promptly after a discontinuance of therapy for a short period of time or by diminishing the usual dosage. Occasionally permanent telangectatic scars may remain.

Summary

1. In this analysis the period of survival is considered from the day of the first roentgen-ray therapy.

2. 736 patients were treated by deep roentgen therapy for carcinoma of the breast, 733 females and 3 males, 652 being considered in our 1 year survival curve.

3. 85% of the patients were above the

age of 40 years.

4. 457 patients (66%) gave histories of symptoms of one year or less.

5. 255 patients (35%) were treated as postoperative prophylactic cases with a 3 year survival of 128 out of 199 treated or 64%, and a 5 year survival of 76 patients out of 158 treated or 48%, and a 10 year survival of 10 out of 24 treated or 41%.

6. 481 patients (65%) were treated as recurrent, metastatic, and inoperable patients with a one year survival of 243 out of 415 treated (59%); 86 patients out of 345 treated surviving 3 years (26%) and 29 patients out of 239 treated surviving 5 years (12%).

7. Metastases were most common in axillary nodes, bone, supraclavicular region, and lungs.

8. Early diagnosis and immediate irradiation therapy following surgical operation gave the best results.

9. Lung fibrosis as a complication can be minimized if the patients are properly rotated under the therapy beam.

Conclusions

Carcinoma of the breast is still a cause of death in a high percentage of the population generally. Early diagnosis of the disease, immediate radical surgery followed by adequate courses of deep roentgen-ray therapy, or therapy preceding operation, has proven to be the most reliable form of treatment known today, and results in various clinics prove a much higher percent 5 and 10 year survival than with surgery alone.

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2. RESULTS OF ROENTGEN THERAPY OF CARCINOMA OF THE PROSTATE

Kenneth L. Olson

The presence of carcinoma of the prostate occurs more frequently than is generally thought, and its incidence increases with age. It has been found in a strikingly high percentage of men over forty years of age at postmortem examination without ever having caused any symptoms of its presence. Rich and Moor each reported separate series of consecutive male autopsies in the same journal. Carcinoma of the prostate was found by Rich in 14% of 292 cases and by Moore in 21% of his series. Neller and Neuberger found carcinoma present in the prostate gland in 25% of men over sixty, and Rich found it in 37% of men between seventy-six and eighty years of age.

The location of the carcinoma is usually accepted as being most frequently present in the posterior portion of the gland. Moore found 73.5% in the posterior portion of the gland; this leaves 26.5% in areas difficult to diagnose by rectal examination. Rich found 65% of this whole series were not diagnosed before death. Diagnosis by biopsy when done at the time of transurethral resection may not be accurate; since the carcinoma may not be reached, and a negative biopsy does not give assurance that carcinoma is not present. Some men advocate aspiration biopsy in cases which have areas in the prostate suspected of being carcinoma, but a negative biopsy report is very unreliable.

Various authors have attempted to correlate the relationship between co-existing lesions in the prostate and the development of carcinoma. Moore and Kahler have each found that the size of the gland or the presence of benign hypertrophy gives no indication as to the presence of carcinoma. Kahler found the presence of atrophy and inflammation as often in his control series as he did in the prostates with carcinoma.

At the University of Minnesota Hospitals, 310 cases of carcinoma of the prostate were treated with roentgen therapy between January, 1927 and December, 1938. Diagnosis was made microscopically in 110 cases and clinically, by rectal examination and x-ray evidence of metastasis, in 200 cases. All but 84 of the 200 cases showed evidence of metastasis before or during the time of x-ray treatments. The 84 cases have been followed and checked after therapy of whom 61 have died with carcinoma of the prostate and 23 are living. From the clinical course and rectal examinations of the living cases, the diagnosis of carcinoma appears to be correct. All the microscopic diagnoses were adenocarcinoma. Kahler found 3% with squamous carcinoma in his series, and he found metastasis present more often when there was a higher grade of malignancy.

Sixty-eight years was the average age of these patients at the time they came to the University of Minnesota Hospitals for treatment. In separating these patients into age groups, 82.3% were between 60 and 80, 4.2% over 80, and 13.5% below 60. The youngest age was 38 years, and oldest was 82 years.

Age	Number	Percent
Under 40	1	.3%
40-49	4	1.3%
50-59	37	11.9%
60-69	131	42.3%
70-79	124	40.0%
80-82	13	4.2%

The onset of symptoms before treatment varied between two weeks and forty years. It is difficult to state definitely the time of onset, because the presence of symptoms of other conditions as inflammation and hypertrophy overshadow the onset of the similar symptoms of carcinoma. The usual complaints were frequency, nocturia, dysuria, hematuria backache and a loss of weight. Symptoms were present one year or less in 52%, between one and two years in 25%, and beyond two years in 23%.

The results of irradiation of carcinoma of prostate are shown in the following tables. Table I shows survival

of 310 cases with all types of treatment in combination with roentgen therapy.

Table I

All Cases Treated Between Jan. 1927 and Dec. 1938

Years		½	1	1½	2	3	4	5	6	7	8
Cases	310	307	298	255	215	172	138	111	85	60	40
Living	310	248	166	101	52	28	13	9	5	1	1
Percent		81%	56%	39%	24%	16%	9%	8%	6%	2%	3%

Table I shows that 16% survived three years, and 8% survived five years. One case is living and well nine years after post-operative prophylactic roentgen therapy. This patient had a radical prostatectomy for benign hypertrophy, and microscopic examination revealed the presence of carcinoma. Barringer has reported a 10% survival at 5 years using x-ray and radon therapy.

In order to give a more accurate value of irradiation, the thirteen cases that received prophylactic roentgen therapy after radical prostatectomy have been eliminated.

Table II

Eliminating Thirteen Cases

Years		½	1	1½	2	3	4	5	6	7	8
Cases	297	294	287	248	206	163	130	104	79		
Living		235	155	94	48	25	12	8	3		
Percent		80%	55%	38%	23%	15%	9%	8%	4%		

Table II shows of the 297 cases treated, 15% survived three years and 8%, five years. All but three of the thirteen cases were operated at some other place, and since the results given in Table I are so slightly changed, some of the thirteen probably had metastasis present at the time of operation.

There were twenty-seven patients who died within two months after the first treatment. Since these cases received treatment as a terminal effort, to relieve pain, they have been eliminated from Table II. This leaves 270 cases with the following result:

Table III

Eliminating Forty Cases

13 who received post-operative prophylactic treatment (prostatectomy)
27 who died two months or less after first treatment.

Years		½	1	1½	2	3	4	5	6	7	8
Cases	270	267	260	226	186	144	114	90	67		
Living		235	155	94	48	25	12	8	3		
Percent		88%	60%	42%	26%	17%	11%	9%	4%		

Table III shows a survival of 17% at three years and 9% at five years. Creevy has reported sixteen untreated cases of which fifteen died in three months, and one living at forty-four months with marked symptoms.

Metastasis to bone was found to be present in 41% of our cases at the time of treatment. X-ray diagnosis of osteoclastic type was present in all these cases, but six had the osteoclastic type also present. The ones with metastasis have been separated from those without metastasis, and illustrated by Table IV.

Table IV

Survival - Metastasis to Bone

Years		½	1	1½	2	3	4	5	6	7	8
Cases	126	125	121	107	92	77	67	56	46	35	24
Living		82	33	14	4	1	0	0	0	0	0
Percent		66%	27%	13%	4%	1.3%	0	0	0	0	0

No Metastasis to Bone

Cases	171	169	166	141	114	86	63	48	33
Living		153	122	80	44	24	12	8	3
Percent		90%	74%	57%	39%	36%	18%	17%	9%

Table IV shows no patient living over three years where metastasis to bone was present, and only four of ninety-two living two years. These received palliative therapy for relief of pain. In the group without metastasis to bone at the time of treatment, 36% survived three years and 17%, five years.

The most common area of bone involvement was to the pelvis and the lower spine. This location of bone involvement accounts for the high frequency of backache which is well relieved by roentgen therapy. Other areas noted were femur, scapula and humerus. Four cases had metastasis to the lungs, but chest films were only taken if some symptoms were present, which accounts for the low incidence of lung involvement. The frequency of occurrence in the pelvis and lower spine has been explained by Warren, Harris and Graves who have reported the path of the metastasis as traveling along the perineural lymphatics directly from the prostate to the bones of the pelvis. Some men believe the microscopic examination of the perineural lymphatics of the prostates removed for benign hypertrophy may reveal an early carcinoma present in some instances.

In order to gain information as to the value of roentgen therapy and as to the dose to the prostate, the cases have been separated into three groups in Table V.

Table V

Survival - Dose of X-ray to Prostate
297 Cases
Eliminating 13 who received post-operative prophylactic treatment

Dose up to 1500 r

Years		½	1	1½	2	3	4	5	6
Cases	158	156	155	144	140	137	120	102	74
Living		119	72	44	26	20	8	6	2
Percent		76%	46%	31%	19%	15%	7%	6%	3%

1500r to 2400 r

Cases	72	71	71	58	42	26	10
Living		62	40	20	10	6	2
Percent		87%	56%	34%	26%	23%	18%

2400 r to 3000 r

Cases	67	67	61	46	24
Living		64	43	30	12
Percent		96%	71%	65%	50%

Table V shows that the first group received up to 1500 r to the prostate; the second, received 1500 r to 2400 r, and the third group received 2400 r to 3000 r. Since the third group could only be followed two years at this time, a comparison of all groups at two years gives 19%, 26% and 50% survivals respectively for each range in dose. An increase in survival occurs with each increase in dose to the prostate. The technique used in each of the three groups was as follows: the first group received anterior and posterior fields giving 800 r to 1000 r, including back scatter to the prostate, in usually four treatments over seven days using 200 kv. with 30 ma at a distance of 70 cm with a half value layer of 1.4 mm copper, giving 60% of erythema at each treatment. The second group received four fields as follows: anterior, posterior, right and left laterals of the pelvis over a period of two to three weeks in eight treatments. The dose varied between 1100 r and 2400 r. All of the third group were given a perineal field in addition to three or five other fields. The smaller sized patients received four fields: anterior, right and left posterior oblique, and perineal. The larger patients received in addition right and left lateral fields. The dose using this method has been about 2500 r in twelve to sixteen treatments, giving 300 r in air to one field each time, and the series extends over twenty-four to thirty-six days. The dose has been increased to about 2800 r or 3000 r to the prostate in the past six months. The half value layer of the radiation used in the third group has been 1.4 mm cu with 200 kv., or 1.75 mm cu with 220 kv. The output has been 20.7 and 17.5 roentgens per minute, respectively, at 70 cm. distance. One notes that the number of days of treatment for each group varied between seven and thirty-six days. The dose for each treatment was smaller, and the number of treatments for each patient was increased in the third group. This extended fractionated method probably improved the results of the last group. There were 105 cases of the 310 that received no radon implants. The cases that had such implants received between 1000 and 3000 millicurie hours, the usual dose being 2500 millicurie hours.

The technique of irradiation has been

changed at various times to try to improve results, and, indications are that the increased dose from 1500 r to about 2500 r increases survival. Because carcinoma of the prostate seems to be rather radio resistant, it is important to give as large a dose as possible by both x-ray and radon irradiation.

The cases that received roentgen therapy were then divided into groups depending on other forms of treatment they had received.

Table VI

Survival - Treatment

Years		½	1	1½	2	3	4	5	6	7	8
X-ray Only											
Cases	105	105	104	88	72	48	35				
Living		75	41	24	12	3	1	(17 living)			
Percent		72%	39%	27%	16%	6%	2.9%				
X-ray - Radon											
Cases	64	63	62	51	49	41	35	30	23		
Living		52	35	19	11	8	4	3	1	(11 living)	
Percent		83%	56%	37%	22%	20%	11%	10%	4%		
Irradiation - Punch											
Cases	93	92	88	77	57	50	40	30			
Living		82	61	40	17	9	3	1	(21 living)		
Percent		89%	69%	52%	21%	18%	8%	3%			
Irradiation - Prostatectomy											
Cases	48	47	45	39	37	33	28	27	24	17	13
Living		39	29	18	12	8	5	5	4	1	1 (11 living)
Percent		83%	64%	46%	30%	24%	18%	19%	17%	6%	8%

Table VI shows forty-eight cases treated by prostatectomy; only three of these were operated at the University of Minnesota Hospitals of which two have lived over five years. The other cases were sent here after operation or after metastasis developed.

The method of treatment at the University of Minnesota Hospitals has depended upon the stage of disease and the amount of retention present. In the very early cases where the carcinoma was confined within the capsule of the prostate gland, a radical prostatectomy was done. As stated previously, only three cases have had a radical prostatectomy since 1930. Young reported only 3.4% of his cases suitable for prostatectomy. Since this method is used in such a small percentage of cases, one must mainly depend on the other methods of treatment. When the carcinoma extends beyond the capsule, the degree of retention governs the type of treatment. If obstruction is slight, then radon is sometimes implanted, and followed by roentgen therapy in six weeks; if retention is severe, a transurethral resection is done to relieve obstruction, and radon sometimes implanted, followed by roentgen therapy in six weeks. The first reaction following and during roentgen therapy is that of swelling of the tissues, and may cause temporary complete retention if obstruction is nearly complete; therefore, these cases have the transurethral resection before roentgen therapy.

From Table VI one notes a better response from radon and x-ray combined, than from x-ray alone. These cases are not comparable since the ones that received x-ray only were ones that had metastasis, and the treatment was given as a palliative measure for relief of pain. The transurethral resection group received x-ray and radon, and shows a little shorter survival, but these cases were more advanced than the cases receiving x-ray and radon alone. Dr. Creevy of the University of Minnesota Hospitals has reported a 46% survival with transurethral resection alone at thirteen months. Table VI shows 69% living at one year and 52% living at eighteen months. Dr. Creevy noted that adding irradiation gives increase in longevity, and reduces the frequency of obstruction. He had seven of thirty-five treated by transurethral resection alone return with obstruction, but none of the sixty-seven who also had irradiation, had recurrence of obstruction. In regard to the degree and duration of improvement of symptoms after irradiation, in this series the duration of improvement lasted about one year in most cases, although in the entire group, there was a variation between two months and several years. There were ten that showed no improvement, but this does not include the twenty-seven that died within two months. The patients showed improvement in frequency, nocturia, dysuria, hematuria, and none had recurrence of complete obstruction, the size of the gland decreasing in most cases. Marked relief of pain from skeletal metastasis was noted especially. A striking example of the effect of x-ray therapy is illustrated by the following case: This man was thirty-eight years of age and had symptoms for two weeks. A cystoscopic examination on 5/3/38 showed an intravesical protrusion of an extravesical lesion on the base and left posterior wall of the bladder. A diffuse tumor about the size of an orange was present, and appeared inoperable as described by the urologist, Dr. Creevy. Then, this man received roentgen therapy from 5/29/38 through 6/1/38, and 27 millicuries of radon were implanted into the prostate through the perineum on 6/10/38. Roentgen therapy was repeated on 10/27/38. On 3/31/39, nine months after the first treatment with roentgen therapy, cystoscopic examination revealed no sign of the tumor, and a normal appearing bladder, and a rectal examination revealed the prostate to be smaller in size. Unfortunately, two microscopic examinations did not reveal any carcinoma. However, Dr. Creevy feels that, clinically, it is carcinoma and that the biopsy tissue did not include the carcinoma.

In going over this group of patients, one becomes convinced that roentgen therapy does benefit the patient with carcinoma of the prostate. Symptoms, if not completely relieved, are lessened to a great extent, allowing the patient to lead a more normal life. When the patient is relieved from the annoying symptom of nocturia and also from frequency he is very grateful. The relief of pain from metastasis is one of the striking results of roentgen therapy. Patients who have been practically bedridden because of pain have been relieved enough to allow them to be up and walking. Any patient with carcinoma of the prostate who develops pain in the lower back should be immediately suspected of having metastasis to the bones, and should have an x-ray of the lumbar spine and pelvis. Occasionally these patients who have an onset with pain in the back are treated for arthritis, subjecting them to unnecessary inconveniences and costs without benefit; whereas an x-ray film or rectal examination would reveal the cause of the pain.

The survival is unfavorably influenced by the high percentage of cases with metastasis. The cases with metastasis should be separated from those without demonstrable metastasis in order to determine the true value of irradiation in prolonging life. The dose of x-ray and radon implants to the prostate should be as large as possible if no bone metastasis is present. If metastasis is found before treatment, then the patient should not be subjected to the heavier doses, but only enough therapy given to make the patient comfortable. The larger doses increase the amount of roentgen sickness, but by watching the patient carefully and regulating fluid intake, adding vitamins, especially the B complex to his diet, one

can get the patient through the period of treatment rather well. Most patients, however, do not have enough sickness to cause them serious discomfort. The optimum dosage has not been established. The toleration of the skin, bowel and bladder, and the general reaction of the patient are the limiting factors of the roentgen dosage given to the prostate.

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3. RESULTS WITH ROENTGEN RAY THERAPY IN HODGKINS DISEASE

Charles B. Craft

Introduction

In 1832, Hodgkin had the distinction of first directing attention to a clinical syndrome, characterized by lymph node enlargement with the frequent accompaniment of splenomegaly. He reported seven such cases, but today only two or three of his original group would come under the classification of Hodgkin's disease. Some thirty years later Wilks (1865) did not only describe cases in greater detail and with more accuracy, but also proposed the idea of grouping those cases with more or less simultaneous disturbances in the lymph nodes and spleen, under the term Hodgkin's disease. Since then numerous classifications and terms have been appended Hodgkin's disease, some 51 according to Wallhauser (1933). Today, especially in the United States, many authors have adopted the term "lymphoblastoma" to designate this large group of conditions characterized by disturbances, chiefly of the lymph nodes, spleen, liver and bone marrow. The undesirability of such an all inclusive group classification is easily understood when it is pointed out that such a classification serves as a "catch all" for this large group of syndromes of unknown etiology, thereby greatly decreasing the stimulus to further study of the specific type of disease, for itself, as well as its relation to others in the group. Therefore, if progress is to be made with regard to etiology, similarities, transitions and interrelations of this large group, it is by separation rather than grouping them under a single classification.

Etiology

Many ideas, theories, investigations and controversies have arisen out of the attempt to determine and ascribe to Hodgkin's disease an etiologic agent. Even today the etiology is far from settled.

Clinical and anatomical evidence tends to support the view that Hodgkin's disease is a systemic disease characterized by the presence of granulomata. The basic histologic studies of Paltauf, and his pupil, Sternberg, led them to consider Hodgkin's disease to be of an infectious nature and the lesions to be of local origin.

Mention of a few of the infectious agents which have received the most favorable comment and study would include the tubercle bacillus in all of its forms, (human, avian, and bovine) as well as the granular form of Fraenkel and Much.

Ziegler, Sternberg, Ewing and others have all found typical tuberculous lesions, both healed and active, in association with Hodgkin's disease. Sternberg was of the opinion that Hodgkin's disease was in reality a modified form of tuberculosis, caused by the tubercle bacillus or a peculiar form of the tubercle bacillus. Ewing states that "in New York, where the disease is very common, tuberculosis follows Hodgkin's disease like a shadow." Most investigators believe the tubercle bacillus to be a secondary invader rather than the etiologic agent. Patients with Hodgkin's disease are very often weak, cachectic, and in poor general health; therefore they are excellent subjects for secondary invaders. In addition, because of the serious damage produced in the lymphoid and reticulo-endothelial systems, in patients with Hodgkin's disease, with the resultant loss of such an important barrier of protection, it is not surprising that a flare-up of a relatively old or recent tuberculous focus may occur, and, terminally, there may supervene an overwhelming acute miliary form of tuberculosis. Bell is of the opinion that the erroneous interpretation of all caseous necrosis as tuberculosis may account for the high incidence of tuberculosis in association with Hodgkin's disease as reported by many authors.

Various diphtheroid bacilli, especially that of Corynebacterium hodgkini, as proposed by de Negri and Mierement, and Bunting and Yates have received consider-

able attention and study. They reported the presence of pleomorphic gram positive diphtheroid bacilli in cultures taken from lymph nodes of patients with Hodgkin's disease. It should be pointed out, however, that diphtheroid bacilli, staplococci, streptococci, and other organisms may be cultured from lymph nodes in entirely unrelated conditions as well as in Hodgkin's disease. The diphtheroids and other organisms represent non-specific secondary invaders, and in the main these organisms today are not regarded as the etiologic agent of Hodgkin's disease.

Recently, Parsons and Poston have reported positive cultures of Brucella organisms, both porcine and bovine, from enlarged lymph nodes in 4 cases of chronic brucellosis, and from other structures in the one fatal case, presenting a histopathological picture characteristic of Hodgkin's disease. The agglutination titres for Brucella, the "brucelleigin" tests and the phagocytic indices were all negative. More recently they have reported positive cultures of Brucella organisms from lymph nodes from 10 of 19 patients with Hodgkin's disease and 3 positive cultures of Brucella organisms from lymph nodes from 3 patients with chronic brucellosis without clinical evidence of Hodgkin's disease. They also report a control series of 67 lymph node cultures of routine biopsies with only one yielding a positive culture. These interesting observations are not presented as a solution to the problem of the etiology of Hodgkin's disease, but rather as a question as to whether chronic brucellosis, existing under certain altered immunologic conditions, may or may not produce a histological picture indistinguishable from that of Hodgkin's disease.

Their material for study has been obtained from subjects residing in a section of the United States where brucellosis is endemic in character, and their findings probably represent the co-existence of chronic brucellosis and Hodgkin's disease in the same patient. Further study, both clinical and experimental, will no doubt tend to clarify the situation.

Twort advocated the theory of a filterable virus, and Gordon and Van Rooyen have been proponents of the theory that Hodgkin's disease is a granuloma of unknown or virus etiology.

The concept of malignancy has many followers (Warthing, Mallory, Bell, Medlar) even though they are somewhat at variance as to the type of neoplasm Hodgkin's disease represents. The concept of malignancy is based on the clinical and pathological picture of an atypical tissue replacing the normal tissue with an eventual mortality rate of 100 per cent. There is characteristic tumor formation, sometimes massive, with infiltrative and metastatic properties. The disease is often found in the liver, spleen, bone, lungs and other organs. The patients, especially the untreated ones, present the signs and symptoms of a progressive fatal malignancy characterized by cachexia, progressive anemia, anorexia, weakness, weight loss and exhaustion, often terminating in a rapid downhill course. No infectious agent has withstood the test of time; sooner or later evidence has been produced to disclaim each organism as the etiologic agent of Hodgkin's disease.

Other theories as to the etiologic agent include (1) animal parasites, (2) ameba, (3) fungus-like bodies. These theories have few advocates and all have been largely refuted, especially by the work of Twort.

Many authors believe Hodgkin's disease to be an intermediate form between a neoplasm and a granuloma.

In spite of the many commendable experimental and clinical investigations, the etiologic agent of Hodgkin's disease has escaped detection.

Symptoms and Physical Findings

Hodgkin's disease may affect persons of any age, race, color or sex. It is a disease primarily of youth and middle life with a peak age incidence between 15 and 35 years of age. The sex ratio is roughly 2 to 1, the males being more com-

monly affected.

The clinical onset is usually insidious. The patients may complain for weeks or even months of weakness, anorexia, loss of weight, cough, fever or pruritis, prior to a gradual painless enlargement of peripheral lymph nodes, most often the cervical. Not infrequently the onset is characterized by the appearance of painless peripheral lymph node enlargement in an apparently healthy individual or following a localized or ordinary infection (tonsillitis, upper respiratory infection, otitis media, infections in and about the oral cavity). Most often the lymph node enlargement is superficial and only one area is involved early, later as the disease progresses other groups become involved. Rarely, if ever, do the nodes suppurate and then only if secondarily invaded. The symptomatology is very variable and practically any and all clinical entities may be simulated. Sometimes an acute form and sometimes a local form is encountered. The acute form is rapid and fulminating, whereas the local form is usually slow in its progress with involvement of only a single site, most often a group of peripheral or mediastinal nodes.

It is not uncommon to elicit symptoms referable to the chest as the chief complaint, namely, cough, dyspnoea, dysphagia, or a sense of pressure within the chest. These symptoms are due to mediastinal lymph node enlargement, lung parenchyma involvement, or both. Extensive mediastinal or lung parenchyma involvement usually leads to dysphagia, dyspnoea, orthopnoea, pleural effusion, cyanosis and venous engorgement with edema of the face or even edema of the upper extremities. These patients are extremely uncomfortable.

A prodromal symptom of importance, often overlooked, is that of pruritis. It may be localized or generalized and there is usually some browning, excoriation and scarring of the skin. Pruritis also occurs during the course of the disease and sometimes because of its intensity, severity and persistence it becomes almost unbearable. Grosz in 1906 reported infiltrations of the skin with the typical picture of Hodgkin's granuloma. These specific lesions have been designated as "lymphogranulomatosis cutis." There are usually no granulomatous infiltrations of the skin accompanying pruritis; however, Bell states that "in the subcutaneous tissues areas of infiltration may be found."

The primary focus may be deep in a fairly large percentage of the cases, involving the abdominal cavity nodes or viscera, the osseous system or the central nervous system. The spleen is palpable in less than one-half of the cases, and when palpable it is usually only moderately enlarged. The liver is palpable even less often than the spleen.

During the course of the disease, one or all of these foci may become involved presenting the signs and symptoms of jaundice, splenomegaly, hepatomegaly, abdominal masses, gastro-intestinal disturbances, pain, spontaneous fractures, paraplegia, Jacksonian epilepsy, mental confusion, headaches, vertigo, dizziness, fever, and pain referable to other parts of the body dependent upon the site or sites of disease process.

Backache is an extremely important symptom and even though physical examination, x-ray and laboratory studies are all negative, the probability is that small or moderately enlarged retroperitoneal lymph nodes are the cause of the backache. There may or may not be pain referable to one or both thighs. Occasionally paralysis of the lower extremities develop, because of invasion of the cord by the disease process, without any retroperitoneal masses having been palpable. Therefore, patients with Hodgkin's disease, presenting the symptom of backache should receive a course of roentgen therapy directed at the retroperitoneal region.

Fever of an intermittent or septic type is usually present sometime during the course of the disease; most often, however, during the latter stage of the disease. Murchison, later Pel and Ebstein called attention to the relapsing type of fever which is observed relatively rarely in patients with Hodgkin's disease.

The blood picture is often characterized by a hypochromic anemia which is usually progressive. There is, as a rule, a moderate leucocytosis, and during the later stages of the disease a polymorphonuclear leucocytosis with a relative or absolute lymphopenia is often encountered. This is considered as a poor prognostic sign and a high eosinophilia is regarded as indicative of a terminal phase. The platelets are reported to be increased in number. The blood picture is not at all typical or diagnostic.

Thus, it is to be noted that Hodgkin's disease is characterized by an extraordinary polymorphism, especially with regard to variations in onset, initial site or sites of involvement, physical findings and blood studies, as well as the successive syndromes which may dominate the clinical picture during the course of the disease.

Pathology

Practically all organs and tissues of the body may become involved in Hodgkin's disease. As a rule only two or three areas are involved in individual cases at a given time.

The lymph nodes may and do vary considerably in consistency. They may be soft and elastic or firm and hard, and both may be encountered in the same group of nodes. These findings are dependent largely upon the progressive changes which have occurred during the evolution of the disease process. The soft nodes are thought to represent an early and cellular stage of the disease and the fibrous or firm node a late stage; however, this is not always the case, and the findings may be the exact reverse.

Grossly the nodes are enlarged with a marked tendency to remain discreet, but rarely and usually late they may become adherent with invasion of the surrounding structures. The capsule is usually thickened, and the cut surface is pale and fleshy or fibrous in appearance. Areas of caseous necrosis are encountered and these areas should not be considered as tuberculous. The absence of epithelioid cells and a sharp line of demarcation at the periphery should rule out tuberculous caseous necrosis.

Microscopically the nodes show very early a preservation of the normal architecture, and the picture is one of lymphoid hyperplasia. Soon this very early stage is followed by a loss of the normal architecture of the node with a prominent increase in the reticular element. This increase in the reticular element is a constant feature and a most important one. There is an increase in the number of small and large lymphocytes, plasma cells, epithelioid cells, eosinophils and polymorphonuclear leucocytes, and especially does the presence of mononuclear and multinuclear giant cells of the Sternberg-Reed type lend a characteristic feature to the microscopic picture. There are many and wide variations in the number and proportion of these cells in various sections taken from the same patient. Obliteration of the sinusoids and areas of necrosis appear. Later there is an increase in connective tissue, and still later the nodes may be composed chiefly of fibrous tissue with very small amounts of cellular content remaining. This sequence of events, leading eventually to fibrosis, does not occur regularly nor in an orderly fashion. Wide variations are found for the same group of nodes, and even within the same node. Structural differences may also be related to various stages of the disease. Even though the histologic picture may appear quite characteristic, in may cases it is often most difficult to make a diagnosis. Not only have pathologists set up different criteria for the diagnosis of Hodgkin's disease but their interpretations may vary widely. In addition, examination of a single fresh specimen, grossly and microscopically, and sometimes even autopsy material often fail to furnish enough evidence to differentiate Hodgkin's disease from lymphosarcoma, aleukemic leukemia, lymphatic and myelogenous leukemia, and occasionally metastatic carcinoma. If the patients have had roentgen ray therapy the task becomes even more difficult and almost impossible.

The spleen though not necessarily enlarged presents microscopic involvement

The spleen though not necessarily enlarged presents microscopic involvement in approximately 80% of the cases. The liver may be enlarged, but not nearly so frequently as the spleen. The liver and spleen usually present discreet areas of involvement which may attain massive proportions. The microscopic picture is quite similar to that noted for the lymph nodes.

The lung parenchyma, pleura, osseous system (vertebra, flat and long bones), central nervous system, gastro-intestinal tract, heart, pericardium, thymus, thyroid and adrenal glands, kidney, urethra, bladder, voluntary muscle, uterus and skin may all show evidence of Hodgkin's disease, with gross and microscopic findings which are characteristic of the disease.

Diagnosis

In view of the fact that the surgical removal of an enlarged superficial lymph node, should there b one, represents at the most a minor operative procedure, it is almost obligatory that a biopsy diagnosis be established. Not only is a correct diagnosis established in the large majority of the cases, but the method of treatment and the prognosis as well. If the site of onset is deep and there are no enlarged superficial nodes the diagnosis becomes extremely difficult. The history, physical findings, laboratory studies, x-ray examinations and even a therapeutic trial of roentgen ray therapy often are most helpful in establishing the diagnosis. Sooner or later, in about 98% of the cases, there appears peripheral lymph node enlargement, and if at that time the diagnosis is still in doubt a biopsy should be carried out in order to establish the correct diagnosis. Lumphosarcoma, aleukemic leukemia, lymphatic and myelogenous leukemia, metastatic carcinoma and tuberculous adenitis offer the greatest difficulties from a differential diagnostic standpoint. Local inflammatory lymph node reactions, generalized acute and subacute lymphadenitis, the lymphadenopathy of syphilis (gumma) and the other lymph-adenopathies are less confusing in both the clinical and microscopic differentiation.

The various forms of splenomegaly are extremely difficult at times to diagnose; however, in splenic anemia, Banti's disease, aleukemic leukemia and Gauchers disease a careful history, physical examination and laboratory studies plus sternal or even splenic punch biopsy aid materially in establishing the diagnosis. Pruritis, especially if there is no well established cause or explanation, should be strongly suggestive of Hodgkin's disease.

Biopsy diagnosis is the method of choice, when feasible, and should be carried out rather than depending upon less reliable methods of diagnosis.

Treatment

Many and varied are the therapeutic measures which have been directed at Hodgkin's disease. Innumerable medications have been tried and all have been found to be unsatisfactory. Arsenic in the form of Fowler's solution is used today by some authors as a therapeutic adjunct in the medical management of their patients.

Surgical attack of the problem has many advocates, both for and against. Yates, and Yates and Bunting, advocate radical operative removal of the diseased lymph nodes and tissue with extensive and adequate regional excision of lymphoid tissue. The operative procedure, if it is to be of any value, must be radical, thorough, and complete, especially with regard to the regional excisions of lymphoid tissue. Radical surgical procedures are most satisfactory and indicative in those cases presenting only single or local areas of involvement, with slow or non-progression of the disease process. Many authors are of the opinion that surgical intervention is of little or no value, and several report cases in which there followed a rapid recurrence at the site of the operation, and a rapid extension of the disease process to other parts of the body following a complete dissection of the tumor and glands in the area. Inevitably there is a recurrence at the site of

operation or in some distant region. If surgical removal of diseased notes, tissue and lymph bearing area is carried out, there should follow, postoperatively, a thorough course of roentgen ray therapy.

Numerous types of serum and vaccine therapy have been tried. Coley advocated the use of mixed toxins of erysipelas and Bacillus prodigiosus. Bunting and Yates, and others, used vaccines of diphtheroids isolated from diseased lymph nodes. Schreiner and Mattick used autolyzed lymph nodes, and Wallhauser and Whitehead used sterile lymph node filtrates. Ovarian extracts and extracts of macerated glands have been tried. Various radioactive substances in the radium and thorium series have been tried. These methods and substances are not and do not constitute a specific elective form of therapy and at the most could serve only as an adjunct in the roentgen ray treatment of patients with Hodgkin's disease. Serum from irradiated patients has been tried but to no avail.

Radium therapy alone and in combination with roentgen therapy have been employed in treating patients with Hodgkin's disease.

There has been no difference demonstrable between radium (gamma rays) and roentgen rays in their biologic action or effect upon the disease process. However, since the advent of more penetrating roentgen rays in conjunction with improvement in apparatus, radium therapy has more or less been limited to those institutions richly endowed with radium.

Radium therapy has the one advantage of being mobile: patients too ill to be removed from their beds or unable to assume certain positions, may be treated by bringing the radium to them.

Some investigators are of the opinion that radium therapy is indicated and advantageous in treating patients in whom a radio-resistant state has developed following the use of roentgen rays. However, the early proper administration of penetrating roentgen rays rarely leads to radio-resistance and then only in the late stage of the disease. It is extremely doubtful if radium therapy could be of any value under these conditions.

The chief objection to the use of radium therapy is the fact that insufficient amounts of energy may be delivered to the deep pathologic foci unless large quantities of radium are available. The superficial adenopathies may be treated quite satisfactorily by means of radium placed at certain distances from the skin. Deep foci receive inadequate amounts of irradiation because the distance from the skin is short and there is a rapid falling off of intensity. This disadvantage is increased if the area or volume of tissues to be irradiated is large.

Radium therapy does have a place in the treatment of Hodgkin's disease, but treatment by the penetrating roentgen ray is the method of choice except in very special cases and unusual circumstances.

Other measures have been advocated and carried out; however, in the main all of these and the above measures have proven to be unsatisfactory and certainly not as effective and specific as has been treatment by means of the roentgen ray.

The employment of roentgen rays in the treatment of Hodgkin's disease began with the clinical reports of Pusey, Senn, and Williams in 1902 and 1903. These authors observed and reported the favorable results and response of patients with Hodgkin's disease, treated by means of roentgen rays.

Heineke, at about the same time, reported the effect of roentgen ray upon lymphoid tissues of guinea pigs and white mice. He demonstrated the extreme sensitiveness of the normal lymphoid tissue in the experimental animal. There occurred, following exposure to roentgen rays, rapid destruction of the lymphoid tissue which, however, was not permanent. After the roentgen ray exposures were discontinued a rather rapid regeneration occurred. Murphy has since shown that large doses of roentgen rays produce great destruction with slow regeneration,

whereas small doses produce slight destruction followed by an increase in lymphocyte production. Warthin, Bunting, Phole and others have confirmed these above observations.

The desirability of producing great destruction of the irradiated lymphoid tissue with the production of necrosis and ultimately complete fibrosis of the involved node or tissue is of prime importance. Therefore, it becomes necessary to administer doses sufficiently large to produce a direct destructive effect upon the lymphocytes, plasma cells, eosinophils, epithelioid cells, polymorphonuclear leucocytes and Sternberg-Reed cells, with the production of necrosis and the stimulation of fibrous tissue reaction and proliferation to complete fibrosis or cicatrization. If complete destruction and fibrosis does not occur, there is the probability that the results will not be permanent, and sooner or later a recurrence will usually take place at the site of irradiation. Essentially the same sequence of events is thought to take place in properly irradiated granulomatous foci in tissues other than lymph nodes. The osseous foci usually respond with an osteoplastic reaction. Occasionally there is no response demonstrable by the radiograph even though there has been an excellent clinical remission. Since the early reports of Pusey, Senn, Williams and others the physical factors employed in the roentgen ray treatment of patients with Hodgkin's disease have varied considerably. The majority of therapeutic radiologists advocate penetrating fractionated doses, rather than single, large, moderate, or small doses given at varying intervals. The roentgen rays should be of sufficient penetration and the total dose high enough to destroy completely all pathologic foci at the deepest point without producing serious damage to the well-being of the patient, the skin, or blood picture. In this clinic the early practice was to administer 600-700 r, in air, in one treatment using 200 K.V.P.; 0.5 mm. cu. plus 1.0 mm Al filter; with a H.V.L. of 0.9 mm. cu. at 60 cm. distance. Since 1926 the technique of irradiation has been changed from time to time in an attempt to improve the results. With this thought in mind it has been the purpose and plan to administer roentgen therapy in such a manner as to destroy as completely as possible all pathologic foci with the resultant and desirable long and frank remissions of the disease process. It is now believed, at this clinic, that the best results are obtained by treating the patients "hard and fast"; that is to say, complete destruction of the pathologic foci with the first course of treatment and the avoidance of further treatment unless recurrence takes place or new areas become involved.

Daily treatments of 200 to 300 r, in air, are given (dependent upon the patient's general condition, site and size of involvement, and size of the field) until a total dosage of 1200 to 1600 tissue r have been administered to each field. The physical factors are 46.4 r per min.; 200 K.V.P.; $\frac{1}{2}$ mm cu plus 1.0 Al filter; with a H.V.L. of 0.9 mm cu., and 60 cm. F.S.D.

In treating unilateral cervical and supraclavicular regions, one to three fields are used dependent upon the size of the lesion. Relatively small posterior, anterior and lateral fields are used in treating the axillary region. Anterior and posterior fields are employed when treating mediastinal and lung parenchyma involvement. Relatively large anterior and posterior abdominal fields are used in treating abdominal cavity viscera and lymph node involvement and a lateral field is added if necessary. For the inguinal region usually only 1 field is employed. In treating sites of osseous involvement 2, 3, or 4 fields are used in pelvic and lumbar spine foci (anterior, posterior, and right and left lateral fields) and in the thoracic and cervical vertebrae a straight posterior and a right and left posterior oblique are employed. The number and size of the fields by necessity are variable from one patient to another and in the same patient at different stages of the disease. Each case is individualized and the total dosage per field, the number and size of fields, the physical factors and the rapidity of treatment are all dependent

upon the general condition of the patient, physical findings, laboratory studies and stage of the disease (early or advanced).

A careful attempt is made to treat the patients in a planned manner. The status of the blood is followed carefully, the patients are encouraged to take adequate amounts of fluid and nutrition. The moderately advanced cases are placed on vitamin B complex (one to two capsules three times daily). Additional vitamins (A, C, & D) are also administered.

It is the practice, at this clinic, to treat only those areas which show definite evidence of Hodgkin's disease and not to employ prophylactic treatment of uninvolved areas, for the reason that it is impossible to predict which area or areas will subsequently become involved. It is felt that the prophylactic treatment of uninvolved areas tends to damage the patient's blood, and general physical condition, and, as a result, subsequent treatment to pathologic foci then becomes more difficult and probably less effective. It is not the practice, in this clinic, to delay treatment until involved areas attain sufficient size to produce pressure symptoms, for the reasons that the patients then are in poorer physical condition, they are less able to withstand a sufficient total dose of roentgen ray therapy, the foci are large and more resistant to therapy and it is often most difficult and impossible to decrease or shrink these foci sufficiently to provide relief before death ensues.

Patients with pleural effusion or ascites are aspirated, should it be deemed necessary, prior to and during their course of therapy. Often the pleural effusion or ascites disappears shortly after therapy with miraculous recoveries having been noted.

Results

The 179 treated cases of Hodgkin's disease herein reported were treated over a 13 year period extending from July 1, 1926 through June 30, 1939. Fifty-two cases of untreated Hodgkin's disease were collected from the autopsy records of the Department of Pathology, University of Minnesota. These 52 cases occurred during a 29 year period extending from June 1, 1910 through December, 31, 1939.

Table I

Sex

Treated Group

Males = 110 or 61.45%
Females = 69 or 38.55%

Untreated Group

Males = 30 or 57.7%
Females = 22 or 42.3%

Table I presents the sex distribution of the treated and untreated groups. It is to be noted that the disease is more prevalent in the male, the ratio being 1.6:1 in the treated group and 1.4:1 in the untreated group. These ratios of males to females are slightly less than the ratio of 2.+ : 1 which are reported by most observers. Minot and Isaacs report that there are relatively more instances of Hodgkin's disease in females among older persons, and since the decade distribution in the untreated group is somewhat higher than usual the low ratio of males to females in this group may be explained.

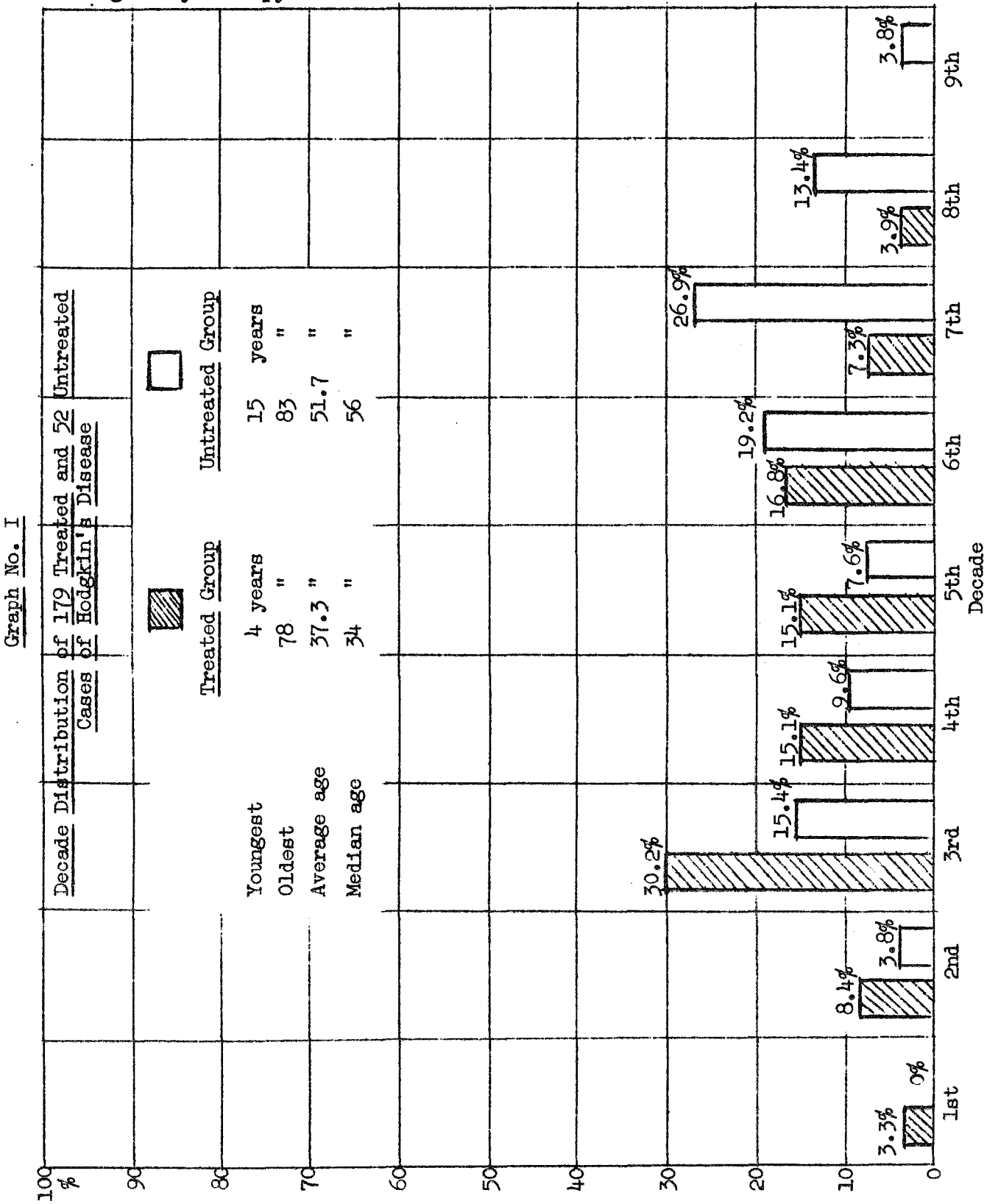
Table II

Method of Diagnosis

No. of Cases		Percentage
127	University Hospital Biopsy	71%
38	Biopsy elsewhere	21%
	(Proven by Biopsy)	92%
14	Clinical Diagnosis	8%

It is to be noted in Table II that 92% of the patients treated by means of

the roentgen ray had a positive diagnosis of Hodgkin's disease established by microscopic study of biopsy material whereas only 8% had a clinical diagnosis. This clinical group consisted of 14 patients in whom the history, physical findings, x-ray and laboratory studies and response to roentgen ray therapy were all consistent with Hodgkin's disease. The average survival of this clinical group was 30.4 months which is considerably less than the average survival of the entire group (Table VII). All of the untreated group were proven cases of Hodgkin's disease at autopsy.



The decade distribution of the treated and untreated groups of Hodgkin's disease is shown in Graph No. I. The peak age incidence in the treated group is found to be in the third decade with a fairly even distribution in the fourth, fifth and sixth decades. The peak age incidence in the untreated group occurs in the seventh decade, with a fairly high incidence in the sixth and third decades. (Forty-three per cent of Sternberg's cases (718) were over forty years of age.) In the treated group the age was taken as that of the first visit to the hospital, whereas the age of the untreated group represents the age at death. This difference in the manner of assigning an age to each patient would bring the average age of the untreated group about 1 year above the proper age for comparison with the treated group. The untreated group, although small, represents Hodgkin's disease in older patients. Craver, Schreiner and Mattick, and Gilbert support the view that Hodgkin's disease runs a more rapid fatal course in patients over 40 years of age. The treated group presents a more normal or frequent pattern of decade distribution. The youngest patient in the treated group was 4 years of age, while in the untreated group the youngest patient was 15 years of age. The oldest patient in the treated group was 78 years of age and in the untreated group, 83 years of age. The average age for the treated group was 37.3 years, and for the untreated group, 51.7 years. The median ages were 34 and 56 years respectively for the treated and untreated groups.

Table III

Site of Onset

Treated Group		Untreated Group	
I. Peripheral Nodes	77.0%	I. Peripheral Notes	46.2%
(1 Cervical Nodes	= 50.8%	(1 Cervical Nodes	
(2 Axillary Nodes	= 16.2%	(2 Axillary Nodes	
(3 Supraclavicular Nodes	= 6.1%	(3 Supraclavicular Nodes	
(4 Inguinal Nodes	= 3.9%	(4 Inguinal Nodes	
II. Chest	= 9.5%	II. Chest	= 11.5%
(1 Parenchymal		(1 Parenchymal	
(2 Mediastinal		(2 Mediastinal	
(3 Both		(3 Both	
III. Abdominal	= 9.5%	III. Abdominal	= 26.9%
(1 Abdominal Masses		(1 Abdominal Masses	
(2 Periaortic Nodes		(2 Periaortic Nodes	
(3 Retroperitoneal Masses		(3 Retroperitoneal Masses	
IV. Skin (Pruritis	= 3.4%	IV. Skin (Pruritis	= 7.7%
(1 Localized		(1 Localized	
(2 General		(2 General	
V. Bone	= 0.6%	V. Bone	= 5.8%
VI. Central Nervous System	= 0.0%	VI. Central Nervous System	= 1.9%

Table III shows the site of onset for the treated and untreated groups. It is to be noted that 50.8 percent of the treated cases had the onset of the disease in the cervical lymph nodes, and a total of 77 percent of the cases were characterized by onset in the peripheral nodes. In the untreated group 46.2 percent began with peripheral lymph node enlargement and 26.9 percent with abdominal visceral, lymph node or retroperitoneal involvement. This high percentage of abdominal cavity and retroperitoneal onset probably accounts for the failure to diagnose Hodgkin's disease prior to autopsy in some of the cases. Sooner or later peripheral lymph-adenopathy occurred and many of these then had a positive biopsy diagnosis established. The other sites of onset are fairly evenly distributed in both the treated and untreated groups. Onset referable to the skin, characterized by pruritis, was noted in 3.4 percent of the treated group and 7.7 percent in the untreated group. The average survival of the untreated group, whether the onset was superficial or deep, was approximately the same, therefore, even though the cases were more likely to escape early diagnosis, the course of the disease was about the same.

Table IV

Sites of Involvement During Course of Disease

Site		Percentage
I. Peripheral Nodes		98.8%
II. Chest	(Mediastinal (Parenchymal (Both	64.4%
III. Abdominal	(Retroperitoneal Nodes (Abdominal Masses (Abdominal Cavity Visceral	46.9%
IV. Spleen		30.1%
V. Skin	Pruritis (Localized (Generalized	20.9%
VI. Bone		13.4%
VII. Central Nervous System		6.7%

During the course of the disease in the treated group, 98.8 percent of the cases ultimately showed involvement of the peripheral lymph nodes, and 64.4 percent showed mediastinal, lung parenchyma, or both, eventually to become involved. The abdominal cavity viscera, lymph nodes or retroperitoneal regions became involved in 46.9 percent of the cases and the spleen in 30.1 percent of the cases. Pruritis occurred in 20.9 percent of the cases at some time during the course of the disease. Only two cases presented evidence of granulomatous infiltration of the skin. Osseous and central nervous system involvement were found at some time during the course of the disease in 13.4 percent and 6.7 percent respectively. These findings are shown in Table IV.

Table V

Survival Rate Hodgkin's Disease (Treated Group)

Years	1	2	3	4	5	6	7	8	9	10	11	12	13	Living
Cases 7	7	7	7	7	7	7	7	7	7	7	7	7	7	
1926 Survival	5	5	4	3	2	1	1	1	1	1	1	1	1	1
Cases 11	11	11	11	11	11	11	11	11	11	11	11	11		
1927 Survival	9	8	7	6	4	3	3	3	3	3	2	2		2
Cases 11	11	11	11	11	11	11	11	11	11	11	11			
1928 Survival	8	7	6	3	2	1	0	0	0	0	0			0
Cases 16	16	16	16	16	16	16	16	16	16	16				
1929 Survival	10	9	5	3	1	1	1	1	1	1				1
Cases 12	12	12	12	12	12	12	12	12	12					
1930 Survival	10	4	4	2	1	1	1	0	0					0
Cases 17	17	17	17	17	17	17	17	17						
1931 Survival	13	9	8	6	5	5	4	3						3
Cases 26	26	26	26	26	26	26	26							
1932 Survival	22	16	11	10	9	5	4							4
Cases 11	11	11	11	11	11	11								
1933 Survival	8	7	6	5	5	3								3
Cases 17	17	17	17	17	17									
1934 Survival	13	10	3	1	1									1
Cases 15	15	15	15	15										
1935 Survival	9	9	7	4										4
Cases 6	6	6	6											
1936 Survival	5	4	4											4
Cases 18	18	18												
1937 Survival	12	10												10
Cases 12	12													
1938 Survival	7													7
CASES 179	179	167	149	143	128	111	100	74	57	45	29	18	7	179
SURVIVAL	131	98	65	43	30	20	14	8	5	5	3	3	1	40
PERCENT	73.2	58.7	43.6	29.5	23.4	18.0	14.0	10.8	8.8	11.1	10.3	16.7	14.3	22.3
LOST 8 OR 4.5	3	2	3	4	4	4	3	4	1	1	2	1	0	

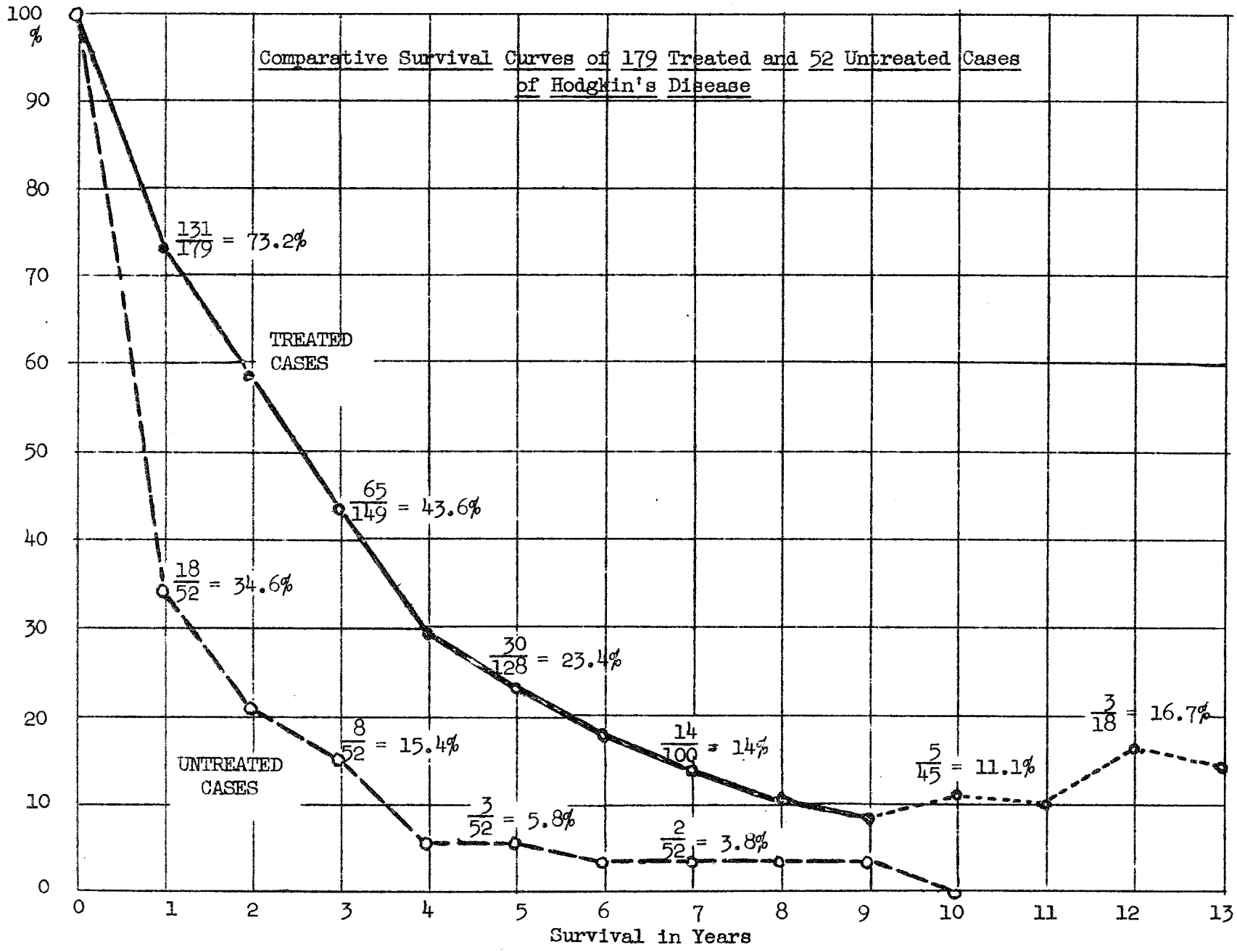
Table V is presented to emphasize the fact that a large series of cases are necessary for study in order to properly evaluate results of roentgen-ray therapy. Attention is called to the years 1929 and 1934. During the year 1929, sixteen cases were treated and only one case (6.3%) survived 5 years and longer. In 1934, seventeen cases were treated and only one case (5.9%) survived four years and longer. In contradistinction the years 1926, 1927, 132, 1933 and 1935 show a much higher percentage of 4 and 5 year survivals. These are shown in Table VI.

Table VI

Year	No. of Patients Treated	4 yr. Survival	Percent	5 yr. Survival	Percent
1926	7	3	42.8%	2	28.5%
1927	11	6	54.5%	4	36.4%
1931	17	6	35.3%	5	29.4%
1932	26	10	38.5%	9	34.6%
1933	11	5	45.5%	5	45.5%
1935	15	4	26.6%		
1929	16	3	18.7%	1	6.3%
1934	17	1	5.9%	1	5.9%

Table V also reveals that 40, or 22.3 percent of the treated group are still alive and only 8, or 4.5 percent could not be followed satisfactorily; that is, until death or July 1, 1939. From Table V the yearly percentage survivals are determined and plotted in the form of a curve in a comparative manner with the untreated group.

Graph No. II


Comparative Survival Curves of 179 Treated and 52 Untreated Cases of Hodgkin's Disease
100 %
90
80
70
60
50
40
30
20
10
0
0
1
2
3
4
5
6
7
8
9
10
11
12
13
Survival in Years
TREATED CASES
UNTREATED CASES
131/179 = 73.2%
65/149 = 43.6%
30/128 = 23.4%
14/100 = 14%
5/45 = 11.1%
3/18 = 16.7%
18/52 = 34.6%
8/52 = 15.4%
3/52 = 5.8%
2/52 = 3.8%

A study of these survival curves, shown in Graph II, reveal a 3 year survival rate of 43.6 percent for the treated group and 15.4 percent for the untreated group. The five year survival rate for the treated group is 23.4 percent whereas it is only 5.8 percent for the untreated group. The curve for the treated group rises after the ninth year, however this portion of the curve cannot be regarded as entirely typical because there are relatively few patients which were treated 10 or more years ago, therefore, only a few patients need live an exceptionally long time in order to give a high percentage of long survivors. For this reason the atypical portion of the curve has been traced with a dotted line. The difference between the 3 and 5 year survival rates, for the treated and untreated groups, are very significant and attest the therapeutic value of roentgen-ray therapy. These significant differences should convince even the most dubious of the effectiveness of roentgen-ray therapy in Hodgkin's disease. The patients not only live longer, but their general well being is tremendously improved in the large majority of the cases.

Table VII

Average Survival Rates
Treated and Untreated Hodgkin's Disease

Treated Group (146)
July 1, 1926 - July 1, 1936

Average Survival		48.3 Months
Average Survival	(Males	46.9 Months
	(Females	49.4 Months

Still Living 22 or 15.1%

Untreated Group (52)

Average Survival		16.6 Months
Average Survival	(Males	15.4 Months
	(Females	17.9 Months

Treated Group (179)
July 1, 1926 - July 1, 1939

Still Living 40 or 22.3%

Table VII presents data relative to the average survival or duration of the disease in the treated and untreated groups. The average survival for the treated group (146 patients) is 48.3 months. This group of patients were treated during the period July 1, 1926 through June 30, 1936 and were followed to death or January 1, 1940. Of this group 22 or 15.1 percent of the patients are still alive. The average survival for the untreated group was 16.6 months. The average survival for those patients characterized by onset of the disease in the peripheral nodes was 17.8 months; chest, 18.7 months; abdominal cavity and retroperitoneal region, 16.4 months; skin (pruritis), 16.3 months; and osseous and central nervous system onset, 4.7 and 5 months, respectively. The cases with osseous (3) and central nervous system (1) onset are too few in number to be of any significance in determining the duration of the disease according to site of onset. Even fewer cases were encountered in the treated group.

The average duration of Hodgkin's disease has been a debatable and an extremely difficult problem to determine accurately. The difficulty has been the proper evaluation of the many factors (age at onset, extent of the disease process, and type of therapy employed, etc.) which play such an important role in the duration of the disease.

A study of a large number of cases by Wallhauser led him to the conclusion that the average survival of patients with Hodgkin's disease was about 24 months. These cases had received therapy, in one form or another, chiefly by means of the roentgen ray or radium thereby affecting the duration of the disease. Ewing states that the average survival is about 18 months.

The high decade distribution of the untreated group, in this series, may account for the somewhat shorter duration of the disease. It should be pointed out that these patients received no roentgen ray or radium therapy. They received general supportive measures; many had biopsies performed; and a few had exploratory operative procedures

carried out. None of these patients had radical surgery as a therapeutic measure.

The average survival of 48.3 months for the treated group (146), with 22 or 15.1 percent of the patients still alive is roughly three times that of the untreated group and at least twice the average survival reported by various authors. Life is definitely prolonged, pain is relieved, long and frank remissions are obtained and many of the patients are returned to full capacity to work by the proper administration of roentgen rays. There should be no doubt that roentgen ray therapy is the method of choice in the treatment of Hodgkin's disease.

A study of the 3 and 5 year survival rates, reported in the literature, show rather conclusively that there has been a progressive and steady increase in these survival rates. Desjardins and Ford (1923) reported a 3 year survival rate of 27 percent and a 5 year survival rate of 9.8 percent for 73 patients who received a variety of treatment but no systematic treatment. Craver (1934) reports a 5 year survival rate of 16.8 percent (125 proven cases) and Leucutia (1934), reporting the final results from 14 institutions based on 805 cases, reports a 5 year survival rate in 15 to 33 percent of the cases and a 10 year survival rate of 8 percent of cases. Gilbert (1939) reports 46 cases with a more than 3 year survival rate of 45.7 percent and a more than 5 year survival rate in 34.2 percent of the cases. Gilbert apparently does not include, in this particular series, cases which were not treated systematically, therefore his survival rates are somewhat higher than most authors report. The University of Minnesota Hospitals cases (128) (1939) include all cases, that is, those receiving inadequate and unsatisfactory treatment and the cases which were not followed were considered as dead at the time they were lost. The 3 year survival rate is 42.1 percent and the 5 year survival rate is 23.4 percent. These survival rates represent the worst possible. This increase in 3 and 5 year survival rates during the past 15 or 20 years is due no doubt to improvement in apparatus, increased knowledge of the biologic action of roentgen rays, individualization of cases and the fact that patients, as a general rule, now seek medical advice earlier plus the conscientious effort of the radiologist to treat the patients in a planned manner with periodic and careful observation after the completion of roentgen ray therapy.

Miscellaneous Data

Interesting information of a miscellaneous character was collected from the treated and untreated groups.

Two cases, proven by microscopic examination of operative specimens and multiple biopsies, not included in the above data, but treated by means of radical surgery and roentgen ray therapy survived 26 years and 16 years and 4 months respectively following diagnosis. Both patients ultimately expired of Hodgkin's disease. Autopsy examination of the patient with a 26 year survival showed Hodgkin's disease of the mediastinal and abdominal lymph nodes, liver, spleen, lung and left adrenal gland.

In the treated group 3 cases had laminectomy performed because of pressure symptoms. Two of these cases are living and well, one 7 years, the other 3 years following operation. One patient expired one month following discharge from the hospital. A bilateral sciatic neurectomy was carried out in one case because of severe intractable pain with excellent results. The patient is alive and free of symptoms 4 years and 4 months after operation.

One case had a subtotal gastric resection because of symptoms and x-ray evidence of a tumor mass in the lower portion of the stomach suggestive of malignancy. The patient is alive and free of symptoms 1 year and 3 months following operation.

Seven cases developed severe jaundice during the course of the disease. Four of these responded well to roentgen ray therapy. All are alive and well, (1) 8 years and 4 months, (2) 4 years and

9 months, (3) 4 years and 3 months, and (4) 1 year and 7 months respectively. Three cases expired, all were moribund when treatment was instituted and little or no treatment could be administered.

A total of 11 cases were considered as moribund when treatment was begun and 8 additional cases received unsatisfactory or inadequate treatment because of their poor general condition, leucopenia, lymphopenia, severe anemia, reaction to the roentgen ray treatment or failure of the patients to report for therapy as requested.

Fifteen or 8.4 percent of the cases were complicated with tuberculosis, 11 of these cases had clinical diagnoses, and 4 were proven at autopsy.

Five cases developed Herpes Zoster as a complication.

One case presented evidence of Amyloid disease of the spleen and liver at autopsy.

Two cases developed a hemorrhagic tendency, late in the disease, characterized by the presence of petechiae and there was frank hemorrhage in one of the cases. One case developed unilateral exophthalmous, there followed a good response to roentgen ray therapy, subsequently the patient developed a bilateral exophthalmus, but no treatment was given because of his very poor general condition.

One patient gave birth to twins, and two other patients gave birth to normal infants after the diagnosis of Hodgkin's disease had been established. There was no evidence of Hodgkin's disease in the offspring.

For the untreated group 11 cases or 21.2 percent presented microscopic evidence of tuberculosis as a complication of Hodgkin's disease. One case developed Herpes Zoster.

Summary and Conclusion

A short review of the literature on Hodgkin's disease is presented.

The theories of the etiology of Hodgkin's disease have been discussed. None of these, as yet, have been proven, therefore, the etiology of Hodgkin's disease must still be considered as unknown.

A plea is made for the separate classifications of that large group of diseases characterized by involvement of the lymph nodes, spleen, liver and bone marrow. If progress is to be made with regard to the etiology, treatment, transitions, interrelations and similarities in this large group it is by separation rather than grouping them under a single classification.

The history, physical findings, laboratory and x-ray studies are all helpful in establishing a diagnosis of Hodgkin's disease, however, an exact diagnosis is desirable for reasons of treatment, prognosis, classification and study, therefore, it is imperative that a biopsy diagnosis, when feasible, be carried out as early as possible.

Many and varied have been the therapeutic measures directed at Hodgkin's disease. Treatment by means of the roentgen ray is the method of choice and such treatment should be carried out in a planned manner. The object of the therapy is to obtain as long and frank remissions as possible with the first course of treatment and the avoidance of further treatment unless recurrence takes place or new foci appear. Variations in the method of administration of roentgen-ray therapy are dependent upon physical status of the patient and extent and stage of the disease. The rays should be penetrating in character. With the proper administration of roentgen rays life is prolonged, there is a gain in weight, appetite and strength, most of the patients are relieved of pain and they are returned to a normal life for many years even though they may eventually die of Hodgkin's disease.

The patients treated at this institution between July 1, 1926 and June 30, 1939 have been statistically analyzed.

The physical factors employed in the treatment of Hodgkin's disease, in this clinic, are 200 K.V.P.; ½ or 1 mm of cu plus 1.0 mm of Al filter; with a H.V.L. of at least 0.9 mm cu; at 60 cm F.S.D.

The average survival of 48.3 months for the 146 treated cases (July 1, 1926 to June 30, 1936) and the 3 and 5 year survival rates of 43.6 percent and 23.4 percent respectively for the 179 treated cases (July 1, 1926 - June 30, 1939) is in marked contrast to the average survival of 16.6 months and the 3 and 5 year survival of 15.4 percent and 5.8 percent respectively in the 52 untreated cases. These results with roentgen-ray therapy are most gratifying and encouraging and emphasize the fact that the method of choice in the treatment of Hodgkin's disease is by means of penetrating roentgen rays.

It is felt that patients with Hodgkin's disease should be followed at all times as carefully as patients with other forms of malignancy. Due to the fact that Hodgkin's disease is not as well known among the laity, as is carcinoma for instance, the proper respect of the disease is not established. Therefore, it becomes the burden of every clinician, surgeon and radiologist to impress upon these patients the importance of frequent follow-up examinations. All too often the patients wait too long before reporting for study and treatment and then it may be too late. The proper administration of roentgen-ray therapy is, in the main, their only hope for prolongation of life as well as restoration to a normal life for many years.

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V. GOSSIP

There are 73 representatives of 65 colleges and universities at the continuation course in Health Problems of College Students at the Center for Continuation Study. Some interesting highlights -- a definite percentage of students are either underweight or overweight. The number remains about the same each year. The underweights are a very tenacious group, as their weight does not change very much even under management. Recent experiments using vitamin B and a control showed that the control group gained more than the vitamin B's. Studies reveal that few if any students injure their vision by excessive study. In myopes there is a better record of scholarship than in any other group (and more visual deterioration). All hearing tests should be done with a audiometer. Studies reveal that the teeth of our students are in worse condition than they were ten years ago. The question of economics is considered. The control of tuberculosis in the student body is an excellent example of what can be done by systematic surveys. Large colleges report fewer cases of valvular heart disease than small colleges. Twenty-five hundredths of one percent of Minnesota students are under treatment for syphilis. "Athletes Foot" is the most interesting skin disease as far as this group is concerned. A surprising number of students with orthostatic albuminuria are found. Only one male student in every 300 has a hemoglobin below 75% while one female student out of every eight has a hemoglobin below 75%, in the entrance physical examinations. Periodic health examinations in the university age group require a good psychiatric approach. Dysmenorrhoea may respond to placebos. Excellent results are being obtained in the management of allergic diseases of respiratory origin. All university housing places have been studied and rated. (Both men and women inspect at the same time in order to get the different angles. An attractive living room gets a higher rating in houses for women.) Women's physical education groups are most interested in teaching proper carriage. Before dental corrections are made after athletic injuries, an impartial observer checks the condition of the teeth in order that the estimate of damage may not be too great. Hygiene courses now correspond most closely to other university offerings so far as teaching is concerned. The University of Minnesota, in spite of, or because of its size, has one of the best student counselling agencies in the country. Health services can be operated efficiently and economically with the type of service offered at the University of Minnesota for about $10 per capita. Certain extras are not included.....The Bulletin today is one of the largest which has been issued for some time. The reports from the Division of Radiation Therapy are always among the most detailed contributions of our group. This is true of cancer reports generally. The Women's Field Army of the American Society for the Control of Cancer collected funds during April in all states in order to further educational work in cancer. In Minnesota the unit is headed by Mrs. Harlow Hansen. Funds collected and methods of education are under the jurisdiction of the Cancer Committee of the Minnesota State Medical Association. Telling and retelling the story of cancer is going on all over the country. Records show that if the present rate of aging in the population continues and if no change is made in the cancer situation, 190 thousand deaths in 1938 will be 192,000 deaths in 1950, and 278,000 deaths in 1970. If this disease had been nonexistent in 1937 the average length of life would have been increased in women 1.82 years and in men 1.17 years. If present conditions are unchanged, cancer will cause the death of 14 out of every 100 women and 12 out of every 100 men. After a certain age is reached, the chance of dying of cancer becomes less. This is largely due to the possibility of dying from other causes. The Citizens' Aid Society of Minneapolis, which gave us the Cancer Institute, are intensely interested in our work in the cancer field. Records indicate that we take care of approximately the same number of Minnesota residents as the Mayo Clinic (about 16% for both of us). The balance are cared for by the rest of the medical profession. There is undoubtedly a great deal of selection based on our radiation therapy department, neurosurgery, and other specialized offerings. (The same differences would also apply to Rochester.).....