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

Hodgkin's Disease

Volume XVII | Friday, March 15, 1946 | Number 17

STAFF MEETING BULLETIN
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INDEX

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William A. O'Brien, M.D.

I. UNIVERSITY OF MINNESOTA MEDICAL SCHOOL
CALENDAR OF EVENTS
March 16 - March 22, 1946
No. 105 Medical Visitors Welcome

Saturday, Mar. 16

9:00 - 9:50 Pediatrics Grand Rounds; I. McQuarrie and Staff; W-205 U. H.

9:00 - 10:00 Surgery-Roentgenology Conference; O. H. Wangensteen, L. G. Rigler, and Staff; Todd Amphitheater, U. H.

9:00 - 9:50 Medicine Case Presentation; C. J. Watson and Staff; M-515 U. H.

10:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; E-221, U. H.

Sunday, Mar. 17

11:00 - 1:50 Obstetrics and Gynecology Grand Rounds; J. L. McKelvey and Staff; Station 44, U. H.

Monday, Mar. 18

9:00 - 9:50 Roentgenology-Medicine Conference; L. G. Rigler, C. J. Watson and Staff; Todd Amphitheater, U. H.

9:00 - 10:50 Obstetrics and Gynecology Conference; J. L. McKelvey and Staff; Interns Quarters, U. H.

12:15 - 1:15 Pediatrics Seminar; Irvine McQuarrie and Staff; 6th Floor Eustis.

12:15 - 1:15 Obstetrics and Gynecology Journal Club; M-435, U. H.

12:30 - 1:20 Pathology Seminar; Pathology of Lupus Erythematosus disseminatus; Dr. J. I. Coe; 104 I. A.

Tuesday, Mar. 19

9:00 - 9:50 Roentgenology-Pediatrics Conference; L. G. Rigler, I. McQuarrie and Staff; Eustis Amphitheater, U. H.

12:30 - 1:20 Pathology Conference; Autopsies; Pathology Staff; 102 I. A.

3:15 - 4:15 Gynecology Chart Conference; J. L. McKelvey and Staff; Station 54, U. H.

5:00 - 5:50 Roentgenology Diagnosis Conference; Drs. Solveig Bergh, Leslie P. Anderson, Stanley Peterson; M-515 U. H.

8:00 - Minnesota Pathological Society; Medical Science Amphitheater.

Wednesday, Mar. 20

8:00 - 8:50 Surgery Journal Club; O. H. Wangensteen and Staff; M-515 U. H.

9:00 - 10:30 Pediatrics Staff Rounds; W-205 U. H.

9:00 - 10:50 Neuropsychiatry Seminar; Staff; Station 60 Lounge, U. H.

11:00 - 11:50 Pathology-Medicine-Surgery Conference; Carcinoma of Cecum; E. T. Bell, C. J. Watson, O. H. Wangensteen and Staff; Todd Amphitheater, U. H.

12:30 - 1:20 Physiology Chemistry Journal Club; Staff; 116 M. H.

4:00 - 6:00 Medicine and Pediatrics Infectious Disease Rounds; W-205 U. H.

Thursday, Mar. 21

9:00 - 9:50 Medicine Case Presentation; C. J. Watson and Staff; Todd Amphitheater, U. H.

12:30 - 1:20 Physiological Chemistry; Cyrus P. Barnum; 116 M. H.

4:30 - 5:20 Ophthalmology Ward Rounds; Erling Hansen and Staff; E-534, U. H.

5:00 - 5:50 Roentgenology Seminar; Review of Literature; Roentgenology Staff; M-515 U. H.

Friday, Mar. 22

9:00 - 9:50 Medicine Grand Rounds; C. J. Watson and Staff; Todd Amphitheater, U.H.

10:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; E-221 U. H.

10:30 - 12:20 Otolaryngology Case Studies; L. R. Boies and Staff; Out-Patient Otolaryngology Department; U. H.

11:50 - 1:15 University of Minnesota Hospitals General Staff Meeting; Holiday.

1:00 - 2:00 Dermatologic Allergy; Dr. Stepan Epstein; W-312 U. H.

2:00 - 3:20 Dermatology and Syphilology; Presentation of Selected Cases of the Week; H. E. Michelson and Staff; W-312 U. H.

1:30 - 2:20 Roentgenology-Neurosurgery Conference; H. O. Peterson, W. T. Peyton, and Staff; Todd Amphitheater, U. H.

II. ROENTGEN THERAPY IN HODGKIN'S DISEASE

T. B. Werner
K. W. Stenstrom

The rapid response of the lymphoblastoma group to X-ray Therapy has been well known for many years. Since the lesions have their origin in lymphoid cells which are the most sensitive of all body cells to roentgen rays, the lymphoblastomas themselves are also very sensitive.[1]

There are certain radiologists who would treat these lesions with very light dosages because even the temporary response is good. There are others who would treat the lesions intensively, approaching dosages used in the treatment of carcinomas. It is likely that the most satisfactory response is obtained with amounts which are somewhere between the two extremes.

A method of treatment has been developed at our clinic which produces results which when analyzed compare very favorably with others so far published. It is our purpose to present statistical data obtained from our records which will give a fairly accurate idea concerning the effectiveness of this method.

A series of 185 cases proven by biopsy will be presented. The biopsy specimens were examined by the department of pathology under the supervision of Dr. E. T. Bell. Another group of 53 cases has been added, in which the biopsies have been examined elsewhere and considered to show Hodgkin's Disease. The slides, however, were not available for confirmation. Clinically these cases had lesions which strongly indicated the presence of Hodgkin's Disease although we cannot claim them as proven cases.

All cases treated in this department from 1926 until December 1942 are included and have been followed until the end of December 1945.

History

The most commonly recognized of the lymphoblastoma group, Hodgkin's[2] Disease, took its name from the man who first recognized it in 1832 as a clinical entity, Sir Thomas Hodgkin. Seven cases of lymphadenopathy, accompanied by anemia and splenomegaly followed by cachexia and death were described by him. Hodgkin felt that the disease was a primary affection of the lymph nodes rather than some secondary infection.

Most of the cases described by Hodgkin are now believed to have been tuberculosis or neoplasm. At least two cases were true examples of the disease and the tissues of one of these are stil preserved in the museum of Guy's Hospita and have been proven by Herpert Fox,[3] with modern microscopic technique, to have the characteristic histological strusture.

In 1856 Sir Samuel Wilks[4] added to the original description of Hodgkin's and pointed out the frequent involvement of liver, kidneys, and lungs. He clearly distinguished Hodgkin's Disease from the leukemias. No detailed description of the microscopic pathology was given until Greenfield[5] referred to the chronic inflammation, marked increase in fibrous stroma, and the large number of multinucleated cells.

Goldmann[6] in 1892 described the importance of eosinophils and Sternberg[7] the characteristic giant cells and areas of necrosis in 1898. Reed[8] in 1902 correlated the pathological findings with the clinical histories. She gave a more accurate description of the cells than Sternberg and recognized the importance of the cells in the diagnosis. The following conclusions were made by her after extensive studies:

1. We should limit the term Hodgkin's Disease to designate a clinical and pathological entity, the main features of which are painless progressive glandular enlargment, usually

starting in the cervical regions without the blood changes of leukemia.

2. The growth presents a specific histological picture, not a simple hyperplasia but changes suggesting a chronic inflammatory process.

3. The microscopic examination is sufficient for a diagnosis. An inoculamay confirm the diagnosis by its negative results (written when its tuberculous nature was upheld by many).

4. Eosinophils are usually present in great numbers in such growths but not invariably. Their presence strengthens the diagnosis.

5. The causative agent is as yet undiscovered. Tuberculosis has no direct relation to the subject.

Wallhauser[9] found about 50 synonyms for the disease demonstrating the confusion regarding classification and etiology. In Germany the disease has generally been known as lymphogranuloma. This term is undesirable until more is known about the true nature of the disease. It is also confusing because there are also other types of lymphogranulomata such as mucosis fungoides, Kaposi sarcoma, Boock's Sarcoid, etc. In this country the term malignant has been added to differentiate it from the other lymphogranulomas and is based on the assumption that the disease is neoplastic. Mallory[10], one of the principal advocates of its neoplastic nature calls it "lymphoblastoma". Other terms used on occasion are "malignant lymphoma", "negokaryoblastoma", lymphoma and lymphadenoma. The latter term seems to be favored by the English. (These names are, however, used in a wider sense and include other entities.)

To avoid confusion, the term "Hodgkin's Disease" is by far the most desirable since it preserves it as a distinct entity apart from the other members of the same large group. Krumbaar[11] advocates use of the term "lymphomatoid diseases" in reference to the leukemias, lymphosarcoma, agranulocytosis, erythroblastosis and other similar diseases.

Etiology

1. Tubercle bacillus. Most of the early authors were convinced that the tubercle bacillus was responsible for the production of the disease. Eight of Sternberg's original 13 cases developed definite tuberculosis.

More recent authors deny vigorously the importance of the tubercle bacillus as a cause. They believe the organism is a coincident or secondary invader. The incidence of occurrence is quite high some authors stating as high as 20%[12]. It is very logical that old tuberculous lesions might become reactivated or new infections occur due to the weak, cachetic state in which patients suffering from Hodgkin's Disease exist.

2. Diphtheroid bacilli are also thought by some authors to be factors in the etiology of the disease, Bunting and Yates[13], DeNegri and Miernot[14], being among the most ardent advocates of this theory.

Bunting and Yates[13] named the organism Bacterium Hodgkini and claimed extracts injected into animals produced Hodgkin's granuloma. Diphtheroid bacilli as well as other organisms are found in lymph nodes due to a variety of conditions. They may be air-borne laboratory contaminants (Wallhauser[9]).

3. Brucella. Parsons and Poston[15] and Wise and Poston[16] reported positive cultures for organisms in the Brucella group in 14 cases of Hodgkin's Disease. Cultures from 67 cases of diseases of the lymph nodes other than Hodgkin's Disease yielded negative results except in one case. No other authors have been able to confirm these findings.

4. Filterable virus. Twort[17] presented a theory advocating the filterable virus on the basis of study of allied disorders such as leukemia of fowls, and pernicious anemia of horses. Gordon[18] injected material from Hodgkin's nodes intracerebrally in animals and produced paralysis and death. He concluded that the filterable virus was

the causative agent. Negative results were obtained with extracts from nodes involved with carcinoma, sarcoma, etc.

Turner, Jackson and Parker[19] demonstrated to their satisfaction that the test was entirely dependent on the presence of eosinophils and was not specific for Hodgkin's Disease. Steiner[20], however, believes that the test is confirmatory if accompanied by histological examination. He admits the test is occasionally positive in nodes involved with lesions other than Hodgkin's Disease but disagrees that eosinophils are the positive factor.

5. Neoplasm is thought by most modern investigators including Warthin[21], Mallory[10], and Bell[22] to be the most likely cause. The high fatality rate and the demonstration of cases in which there is a delayed interval between the so-called primary lesions and metastatic lesions, is somewhat convincing. The absence of any proven infectious agent leads one to believe more strongly in its neoplastic nature.

Symptoms and Physical Findings.

The symptoms are variable, depending on the stage of progression at the time of the patient's first visit to the doctor. The only complaint may be palpable cervical or axillary lymph nodes.

There may be systemic symptoms of greater or lesser degree, such as fever, weakness, anorexia or loss of weight. Frequent coincident infections occur, such as tonsillitis, upper respiratory infections, otitis media, and infections in the mouth. These may produce adverse effects.

Weakness is not infrequently the first symptom and in the absence of obvious lymphadenopathy may be very difficult to evaluate. A careful search should be made for enlarged lymph nodes and abdominal masses. An x-ray film of the chest might show lesions characteristic of this disease.

A dry, hacking type of cough frequently is the first indication of involvement of mediastinal nodes. Dyspnea, cyanosis, dysphagia, occur later and indicate obstruction due to marked mediastinal enlargement or extension of lesions into the pulmonary parenchyma. Pulmonary involvement is often accompanied by fever. Venous engorgement may also occur and is a very distressing symptom.

Nausea and vomiting do not necessarily suggest occurrence of the disease in the gastro-intestinal tract but can best be explained by the systemic effects. Abdominal pain is usually an indication of enlarged abdominal nodes with pressure effects. The hemorrhagic diathesis present in the disease might produce melena and hematemesis.

Occasionally paralysis of one or both lower extremities occurs as a result of vertebral or extradural involvement. Collapse of the vertebrae may occur, however, without paralysis. Enlarged retroperitoneal nodes are the commonest cause of backache. Backache is a sufficient indication for x-ray therapy to the retroperitoneal region in the presence of Hodgkin's Disease, even in the absence of other positive signs.

Pain usually occurs in bone lesions before these are actually demonstrable on the x-ray film. In 13 cases reported by Jackson and Parker,[23] pain was present for 2 - 12 months before positive roentgenograms were obtained in spite of repeated examinations. Conversely, large bone lesions have been found without symptoms.

Pruritis often occurs early in the disease, and its presence is disturbing. It can be severe enough to cause marked excoriations of the skin from scratching. Often there is no visible change but on microscopic examination, many of these cases will show some degree of lymphocytic infiltration. The more specific lesions have been designated as "lymphogranulomatosis cutis" and have a nodular or ulcerated appearance. Pruritis is occasionally the first symptom and any case of ideopathic pruritis should be examined closely for

evidence of enlarged lymph nodes.

Pathology

According to Bell,[22] the lymph nodes on gross examination are enlarged, pale and firm, and the consistence is fleshy or fibrous. They have a definite tendency to remain discrete and seldom become matted together. The same appearance is seen on gross examination in aleukemia and lymphosarcoma. On section, areas of caseous necrosis are rather common in the lesions of Hodgkin's Disease. This finding has been responsible for the suggestion of tuberculosis being the cause, but the necrosis is actually due to the disease itself.

The microscopic structure is widely variable in different cases and to a lesser extent in various lymph nodes from the same individual. There are also some structural differences related to the stage of the disease.

There are certain distinctive features of Hodgkin's Disease. There is an increase in the number and size of the reticulum cells, often with the formation of giant cells of Dorothy Reed type, increase of reticulum fibers with the formation of areas of fibrosis, obliteration of the sinusoids, eosinophil cells, areas of necrosis and increase of lymphoid cells. In thpical cases there are Dorothy Reed cells, and areas of fibrosis.

Jackson and Parker[24] would restrict the diagnosis of Hodgkin's Disease to cases showing Dorothy Reed cells. Bersack[25] states that the Reed cells are present only in later cases. In many cases, even after careful examination, Dorothy Reed cells have not been found, but on specimens taken from the same patient after further progression of the disease, the typical findings were present.

Enlargement of the lymph nodes with obliteration of the sinusoids is of great diagnostic importance. The areas of necrosis can be distinguished from tuberculosis by their sharp demarcation from the surrounding tissue and the absence of epithelioid cells. Often there are large numbers of eosinophil leucocytes in the cellular areas.

The cellular forms of Hodgkin's Disease blend with leukemia. There is also a blending with lymphosarcoma and leukemic reticulo-endotheliosis. A single node is often insufficient for differentiation and difficulties are even encountered at autopsy.

Occasionally one of the lesions of Hodgkin's Disease grows rapidly and exhibits the histological structure of a sarcoma.

Jackson and Parker[24] present a new concept of the disease. They describe three types each of which has a distinct appearance pathologically and has a different prognosis.

According to these authors, the paragranuloma is the early variety and its main feature is lymphoid hyperplasia, the principal cell being the adult lymphocyte. Reed-Sternberg cells are present in small numbers. It is considered rather benign but it may progress to the next type called Hodgkin's granuloma.

In the granuloma group, the distinguishing features are eosinophilia, necrosis and fibrosis. This is the group most commonly seen in clinical practice and presents a serious prognosis.

The third group, Hodgkin's sarcoma, is a very malignant type. The principle features are the presence of large tumor cells and Reed- Sternberg cells with only occasional necrosis and relative rarity of the characteristic cells in granuloma. It is rapidly growing and fatal in a short time. It is most commonly primary in the retroperitoneal lymph nodes and gastro-intestinal tract but rather uncommon in the peripheral nodes.

Jackson and Parker place great significance in the histological appearance as an indication of the prognosis of the disease. Numerous authors dispute

this, among them Slaughter and Craver,[26] who reported 14 cases of Hodgkin's sarcoma, 5 of whom survived over 3 years, 3 of these survived more than 5 years, and one survived over 7 years. This is a good survival rate for any group of Hodgkin's Disease. The patients in their general series who survived less than 6 months, presented no consistent histological picture.

Diagnosis.

1. Biopsy. A positive diagnosis of Hodgkin's Disease depends entirely on its histological appearance. Any lymph node which is definitely enlarged can be selected, but the largest is probably the best choice since sections can be made from more widely separated areas.

2. In a smaller percentage of cases no enlarged lymph node can be palpated and onset may be in the mediastinal nodes or abdominal nodes. In the mediastinal cases, examination by means of x-ray will be of great assistance in determining the site and extent of the lesion. In these cases a tentative diagnosis of lymphoblastoma can be made along with findings obtained by history, physical examination and laboratory studies, but it may be impossible to determine the subdivision. X-ray therapy should be suggested as a therapeutic test to determine response which occurs quite rapidly in lymphoblastomas.

3. Certain of the clinical findings commonly found in Hodgkin's Disease such as pruritis, Pel-Ebstein fever, lymph node enlargement, should lead one to strongly suspect the diagnosis. Eosinophilia is a suggestive differential sign from those diseases not having this finding.

Differential Diagnosis

It is sometimes difficult to differentiate Hodgkin's Disease from the other members of the lymphoblastoma group even when a biopsy has been obtained; viz. leukemias, lymphosarcomas. Metastatic carcinoma is often very difficult to differentiate from Hodgkin's Sarcoma. Tuberculous adenitis also provides considerable trouble because of its necrosis, fibrosis and similarity of constituent cells.

The other types of lymphadenopathy accompanying local or generalized inflammatory diseases are less confusing in the clinical and microscopic differentiation.

When an enlarged spleen is the outstanding feature, the diagnosis may be obscure. Most other commonly recognized types of splenomegaly are Banti's syndrome, splenic anemia, Gaucher's disease, thrombocytopenic purpura, amyloid disease, syphilis, malaria, leukemias, etc. In many cases, the diagnosis is obvious from other clinical and laboratory findings, but biopsy is necessary for definite confirmation.

In those cases with bone involvement the appearance might simulate the findings in multiple myeloma. The finding of the characteristic Bence-Jones protein, elevated globulin, and most diagnostic bone marrow studies are conclusive in myeloma.

Incidence

Race. Hodgkin's Disease attacks individuals of every race without discrimination. In America it affects negroes and whites to about the same extent.

Sex. The disease is more prevalent amongst men than in women. In Wallhauser's[9] series of 1447 cases collected from the literature, the incidence was about 70% in males and 30% in women. In our series of 185 cases of proven Hodgkin's, the incidence amongst men was 62.2% and in females, 37.8%. (Table I).

Age. In most series reported, the onset in the greatest number of cases occurred in the third decade of life. In our series, as shown in Table II, the greatest percentage (27%) were in the third decade, compared with 12.4%

Table I

HODGKIN'S DISEASE

185 Cases with Positive Biopsy

Sex	Number	Per Cent
Male	115	62.2
Female	70	37.8
Total	185	100

Table II

Age Distribution - 185 Cases HODGKIN'S DISEASE - Postive Biopsy

	0-10	11-20	21-30	31-40	41-50	51-60	61-70	71-80	81-90
Number	6	23	50	29	30	24	16	6	1
Percent of total in each decade	3.2	12.4	27.0	15.7	16.2	13.0	8.7	3.2	.5
Duration of life from 1st treatment for each decade	36.5 mos.	53.1 mos.	33.4 mos.	44.5 mos.	42.5 mos.	15.9 mos.	19.3 mos.	16.6 mos.	1 mo.

Average survival time - 185 cases from time of 1st treatment = 33.0 months.
Average interval from time of onset until 1st treatment = 15.5 months (173 cases).
Median age = 34 years.
Average age = 38.2 years.

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in the second decade and 15.7% in the fourth decade. Extremes of ages in our cases were 5 to 81 years and the average age was 38.2 years. The age in this series refers to the age at the time of treatment.

Site of onset. As in other series, most of the cases had their origin in the peripheral lymph nodes. (Table III).

Table III

Site of Initial Involvement - HODGKIN'S DISEASE
185 Cases with Positive Biopsy

Site	No.	%	Site	No.	%
Cervical lymph nodes	112	60.5	Skin	9	4.9
Axillary lymph nodes	19	10.3	Bone	3	1.6
Supraclavicular lymph nodes	4	2.2	Breast	1	.5
Inguinal lymph nodes	8	4.4	Generalized	6	3.2
Mediastinum	11	6.0	Thyroid	1	.5
Mediastinum plus Pulmonary Infiltration	3	1.6	Tonsil	1	.5
Abdominal nodes	7	3.8	Total	186	100.

The disease began in the cervical nodes in 60.5% of the series, and in the axillary nodes in 10.3%. Some of the more unusual sites of origin were the breast, thyroid and tonsil, each involving one case; the bone in 3 cases, and the skin in 9 cases. The latter includes those cases in which pruritis was the first symptom noted.

Many cases which have their origin in deeper areas such as the abdomen are not discovered until peripheral node involvement has occurred, and are then mistakenly thought to have begun in these peripheral areas.

Site of involvement. Since Hodgkin's Disease is histologically a disease of the reticulo-endothelial system, it may be found in almost any organ of the body. The peripheral lymph nodes are the most frequently involved. In our series (Table IV), 98% of the cases showed some type of peripheral lymphadenopathy at some time in the course of

Table IV

Site of Involvement - HODGKIN'S DISEASE -
185 Cases with Positive Biopsy

Site	No.	%	Site	No.	%
Peripheral lymph nodes	181	98.	Liver	19	10.2
a. Cervical	154	83.	Omentum	1	.5
b. Axillary	120	64.5	Parotid Gland	1	.5
c. Supraclavicular	38	20.5	Pancreas	5	2.7
d. Inguinal	81	43.6	Stomach	6	3.2
Thoracic	123	66.1	Adrenal	3	1.6
a. Mediastinal lymph nodes	113	60.7	Thyroid	3	1.6
b. Parenchymal involvement	56	30.1	Eustachian tube	1	.5
c. Pleural effusion	18	9.7	Face	6	3.2
Abdominal (Abdominal plus (Retroperitoneal	100	53.8	Breast	6	3.2
			Kidneys	6	3.2
Spleen	57	30.6	Peritoneum	1	.5
Skin	31	16.7	Gall-bladder	1	.5
Bone	37	19.8	Tonsil	1	.5
Nervous System	4	2.2			
Muscle	8	4.3			

the disease. The cervical nodes were involved in 83% of the cases, followed by axillary in 64.5%, inguinal in 43.6% and supraclavicular in 20.5%.

In Craver's[27] series of 220 cases, lesions of the lung were present in 29% of the total number. In our series of 185 proven cases, intrathoracic lesions were present in 66.1% of the cases, which appears to be much higher than most comparative series. Of the total cases, mediastinal lesions were present in 60.7% and parenchymal lesions in 30.1%. In all these cases the involvement was verified either by chest roentgenograms or at autopsy. Pleural effusions were present in 9.7% of the cases which is somewhat less than in most other groups.

In Wright's[28] series of 60 intrathoracic cases, x-ray examination showed involvement of the mediastinal nodes in 57 cases. Twenty-one cases had parenchymal lesions and there were 17 cases of pleural effusion.

Abdominal manifestations may resemble tuberculous peritonitis, with a serous or rarely chylous ascites. Retroperitoneal involvement may be revealed by the results of pressure on the vena cava, bowel or nerves. Jaundice may result from pressure on the bile ducts

the degree of which may fluctuate. It is impossible in many cases to distinguish involvement of abdominal from retroperitoneal node involvement; therefore all of our cases have been classified as having abdominal node involvement. In most of these cases palpable masses were present in the abdomen. In a smaller number, palpable masses were not present but symptoms of abdominal involvement were extremely suggestive in cases where a diagnosis of Hodgkin's Disease had already been made from biopsy of a peripheral lymph nodes. There was involvement of the abdominal and retroperitoneal nodes in 53.8% of the 185 cases.

The spleen was enlarged in 30.6% of the 185 cases. Enlargement of the spleen was accepted as sufficient evidence in a case of known Hodgkins. Many authors state lesions in the spleen occur in as many as 60 - 70% of the cases, usually being enlarged by the Hodgkin's proliferation either diffusely or with local foci appearing grossly yellow or gray, suet-like.

Bone lesions are most often osteolytic and occur in the ribs, sternum, vertebrae, pelvis, humerus or femur. These lesions are frequently single and appear on the roentgenogram as rarefied, cystic areas, sharply demarcated. Occasionally an osteoblastic type is present and involves more than one bone. This type responds less satisfactorily than the osteolytic type. In our series bone lesions, demonstrable by x-ray examination, were present in 19.8% of the cases. In a series of 257 cases reported by Vieta et al,[29] bone lesions were present in 14.8%; 58% of the lesions were of the mixed variety; 28% were entirely osteoclastic; 14% were purely osteoblastic.

The bone lesions may develop by enlargement of foci in bone marrow or by extension of adjacent foci infiltrating or pressing on bony structure. All bone lesions in our cases were demonstrable by x-ray examination or at autopsy.

Nerves and spinal cord can be similarly involved by the spreading lesions, giving pictures difficult to differentiate from neoplastic or other diseases. Herpes Zoster is a fairly common complication of Hodgkin's Disease (6 cases in our series). Lesions in the nervous system were present in 4 or 2.2% of our series.

Pregnancies occurred in 4 cases at some time following treatment. In all, 6 children were born to 4 of the patients.

Tuberculosis in an active or inactive state was present in 6 cases. Tuberculosis and Hodgkin's Disease are not infrequently coincidental, as described by Sternberg.[7]

An unusual site of involvement is the breast, according to Adair and Craver.[30] Only 8 cases were reported in the literature and 5 cases were added by these authors, producing a total of 13 cases. One of our cases developed a breast lesion during the course of her disease, and the breast was amputated. Histological examination revealed the typical structure of Hodgkin's Disease. One male patient, aged 27, developed a diffuse infiltration of the entire breast which responded well to therapy. Two patients had nodules in the breast. Another had a large mass in the breast and an additional one had a diffuse enlargement of the whole breast. While only one case had a positive biopsy of the breast lesion, the presence of definite masses or infiltration of the breast which responded to x-ray therapy in cases of known Hodgkin's, is strong evidence in favor of involvement.

Treatment

Irradiation either by X-rays or radium is by far the most effective method in the treatment of Hodgkin's Disease. The prognosis of Hodgkin's Disease for cure is very uncertain and the term "survival rate" seems the proper one to use in respect to this disease.

Hodgkin's Disease is so varied in its manifestations that it is necessary to treat each case individually. Different parts of the body should be treated in different ways, depending upon the

accessibility of the involved nodes. Advanced stages also require some modification. A few basic principles are followed, however, in all cases.

Usually more than one node in a chain is involved and the whole group should be treated as a unit. For example, if cervical nodes are involved on one side it would seem advisable to include the supraclavicular and submaxillary nodes in one field. The mediastinum also should be treated as a whole, rather than only the area where there is a visible mass.

The enlarged nodes usually begin to respond within a few days after the first treatment and may disappear after a relatively small dose. It is likely, however, that some of the abnormal cellular structure indicating activity, still remains in the nodes and a local recurrence will soon be noticed. The recurrences seem more radio-resistant and it is therefore advisable to give a heavier dosage during the initial series to prevent these recurrences. The series should be given in a relatively short time to produce the maximum effect and 14 days has been arbitrarily chosen as the upper limit. If it can be given in a shorter time without too much ill effect, the results may be even further improved.

A dose of more than 1000 tissue roentgens is given in almost all cases and the dose in some cases may be as high as 2000 tissue roentgens. It is rarely increased to more than than this amount.

In the case of cervical nodes, 900 roentgens in air is given to each of three fields including an anterior, posterior and lateral field. In the case of the mediastinum, 1200 to 1500 roentgens in air, to each anterior and posterior field, is, in our opinion, within the proper range of dosage.

Very large masses of long standing are usually more resistant to radiation than smaller, more recently enlarged nodes and should be treated more heavily. The recently enlarged nodes should, however, be given a certain minimum dosage even though they may respond and return to normal size before the intended amount is given.

It is impossible to predict the site of involvement which may occur in the future. Isolated areas may become involved such as the scalp or extremities, while the larger chains of nodes are not affected. For this reason, we believe that prophylactic irradiation is contraindicated.

The most favorable cases are those in which only one chain of nodes is involved and thorough irradiation is given after a biopsy has been taken. Slaughter and Craver[26] refer to local resection followed by irradiation as a very successful method in this type of case. They reported 5 cases treated in this manner with very satisfactory results. The survival period in these cases was 5, 6, 8, 11 and 11 years. (Fingi[31] stated that the longest survivals were in patients with strictly localized disease who were treated with heavy dosage even after regression of the nodes.)

These results suggest that Hodgkin's Disease may start as a localized process, which, if arrested, might delay development of a generalized disease.

It is reasonable to suppose that heavy X-ray dosage would produce as effective a result as surgery in the case of radiosensitive lesions such as the lymphoblastomas. In most cases X-ray therapy should be more effective since all the nodes in the chain would be included.

O'Brien[32] observed one patient in whom there was surgical excision of nodes in 1920 from the cervical region. Nineteen years later there was a recurrence in the supraclavicular nodes were removed with good results. Histological examination revealed Hodgkin's Disease.

When several chains of enlarged nodes are present, the chain causing the most symptoms is treated first. The full dose is given to this area before treatments to the next area are started. If the patient's condition permits, the second group may be started before completion of the first.

An interesting observation in the treatment of some cases with generalized manifestations, particularly pruritis, fever and weakness, is the marked response after treatment of the local lesions. The pruritis often clears rapidly and the patient's general condition is usually much improved as the local areas respond.

A 200 or 220 KV and $\frac{1}{2}$ mm. Cu + 1 mm. Al filter have been used for the peripheral lesions in our cases. The half value layer was .9 or 1.3 mm. Cu respectively. For the deeper lesions the filter was increased to 1 mm. Cu + 1 mm. Al, the half value layers being 1.4 or 1.7.

Total Body Irradiation

The principle of small doses of irradiation to the entire body, or spray irradiation, has been described by Dessauer[33] in 1907, Chaoul and Lange[34] in 1923. The latter used it in 12 cases of Hodgkin's Disease with varying degrees of success. A similar method was introduced at Memorial Hospital, New York, in 1931 by Heublein,[35] and has been called the "Heublein method". Only moderate doses of x-rays to the entire body in the human would, of course, produce very deliterious effects. In the animal, one erythema dose produced rapid death. Small doses, however, often resulted in considerable reduction in size of the tumor growth.

Heublein, in collaboration with Craver, and Failla of the Memorial Hospital, devised a method of treating patients with prolonged continuous irradiation with hard roentgen rays at low intensity at long target-skin distance. Dosage was about 17 r/day at a rate of .86 r per hour for an average dose of 100 r. In treating the cases of Hodgkin's Disease, no cases were treated with the Heublein method alone, because it was considered unwise not to give additional local therapy to each group of nodes.

Ninety-four cases[36] were treated with local therapy and body bath. The average survival after combined radiation therapy at the Memorial Hospital is 42 months. For all cases, irrespective of treatment, the average is 34 months. In the Heublein series, the 5 year survival rate was 24% which was an improvement of 6.2% over the series of all Hodgkin's treated at that clinic.

The following conclusions were reached regarding the Heublein theory:

1. Body bath alone is not sufficient to produce lasting results.
2. The greater the amount of previous therapy the poorer the response.
3. Terminal cases of Hodgkin's were unafrected.
4. The first few treatments were the most beneficial.
5. Maximum improvement resulted where local disease was first controlled by local therapy.

Certain reactions may occur to x-ray body bath, particularly gastro-intestinal disturbance, weakness, apathy, fever, purpura, or unfavorable blood changes. In patients who have had recent large doses of x-ray and have leukopenia, body bath should be given with great caution.

Body bath is a procedure which is extremely impractical in most clinics according to the Heublein method. Limitations in the number of x-ray machines prevent usage of the procedure, since in the Heubelin method, one machine is devoted daily to the treatment of only two patients for periods of 20 hours or more.

Routine use of this method has not been tried at our clinic. Spray irradiation has been given here at a much higher rate per minute to a total dosage of 30 r at a target-skin distance of 140 cms., repeated for as many as 2 or 3 doses in a series. Two cases showed remarkable improvement following body bath and the improvement lasted long enough so that benefit from local therapy was obtained. However, in most cases where this type of therapy has been given the patients were terminal and were unimproved.

Treatment according to Systems

In all locations where possible, 900 r in air should be given to each of three areas. This is applicable in the case of the cervical regions. Where there is bilateral cervical involvement, therapy should be administered with considerable care in directing the x-ray beams in order to prevent too much concentration in the central area of the neck. Extreme discomfort can be produced by excessive reaction in the pharynx or esophagus, resulting in dysphagia, hoarseness and dryness of the throat. This reaction reaches its maximum in approximately 3 weeks. Rather severe skin reaction can occur from the cross firing of carelessly directed beams in these cases. In order to avoid these complications the beams which ordinarily are directed transversely are aimed obliquely.

Pulmonary involvement is often accompanied by rather severe dyspnea because of bronchial obstruction due to enlarged mediastinal nodes. In these cases, it is considered unwise to administer the usual 250-300 roentgens/air to the mediastinum in one treatment, because edema of the bronchi may occur after the first or second treatment. The edema added to the constriction already present would result in serious consequences. Hence 50 - 75 r/air should be given on the first treatment and increased gradually with following treatments until the patient can tolerate average doses. The obstructive lesions usually respond rapidly with marked relief in dyspnea.

Cases which have received previous therapy to the mediastinum or lungs might conceivably develop pulmonary fibrosis when given more therapy in the same regions. While this complication is not too common, it should be kept in mind when interpreting follow-up roentgenograms of the chest. The fibrosis can very conceivably be misinterpreted as recurrence of Hodgkin's infiltration, resulting unjustifiably in further therapy to this region.

Treatment to the abdominal nodes and retroperitoneal lymph nodes results in certain complications which, however, are usually not too serious to prevent completion of a full series. Nausea, vomiting, diarrhea and other gastrointestinal symptoms are quite common, especially when the treated areas are quite large. If widely separated masses are present, they are best treated separately. Back pain in a known case of Hodgkin's is a sufficient indication for therapy even in the absence of palpable masses.

Results of Treatment

Earlier reports show the duration of life following the onset of the disease was very short, although some cases have been known to live for 5 to 10 years without any therapy. In general, the survival period in children appeared to be considerably shorter, the average being under 20 months.

Following the advent of x-ray therapy, there was a distinct increase in the survival period by as much as 1 - 2 years. According to Krumbaar[10], records at the University of Pennsylvania show the 5-year survival period to be 15.4%, and 10 years, 6%, following the method of Pendergrass. In this series, the longest period of survival was in one case still living after 22 years.

In Craver's[26] series of 265 cases, there was a 5-year survival period of 17.7% and a 10-year survival of 3.4%. The average survival of all cases in their series was 33.8 months from the beginning fo x-ray therapy. Another group of 94 cases, which was given the Heublein method of therapy, presented an average survival rate of 42 months from the onset of therapy and a 5-year survival rate of 24%. Most of these cases were apparently included in the 265 cases reported by Craver and Slaughter. It is obvious that the 265 cases would not have as good a survival rate without the inclusion of these 94 cases. The series of 94 cases probably presents the most favorable of any report in the literature.

In our series of 185 cases proven by biopsy (Table V), the 5-year survival rate was 21.0% and the 10-year survival rate 8.0%. The average survival rate

Table V

Survival Rate after 1st Treatment - HODGKIN'S DISEASE - Positive Biopsy Cases

Year	No. of Cases	Years of Survival 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Living
1926	2	2	2	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0
1927	3	2	2	2	1	0	0	0	0	0	0	0	0	0	0	0	0	0
1928	5	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1929	8	4	3	3	2	1	1	1	1	1	1	1	1	1	1	1	1	1
1930	7	4	2	1	1	0	0	0	0	0	0	0	0	0	0	0		0
1931	16	12	7	6	5	3	3	3	3	3	2	2	1	1	1			1
1932	18	13	11	6	6	4	3	3	2	2	1	1	1	1				1
1933	15	8	7	7	7	7	5	3	2	2	2	1	1*					0
1934	14	11	7	5*	1	1	1	1	1	1	1	1						1
1935	14	8	8	6	5	4	2	2	2	2	1							0
1936	5	2	2	2	2	2	1	1	1	1								1
1937	15	9	7	6	6	4	4	4	4									4
1938	12	10	8	6	4	1	1	1										1
1939	13	4	3	1	1	0	0											0
1940	13	7	6	6	6	6												6
1941	10	6	5	5	5													5
1942	15	7	5	4														4
Cases	185	185	185	185	170	160	147	134	122	107	102	88	74	59	41	25	19	25
Survival		111	85	67	53	33	21	19	16	12	8	6	4	3	2	1	1	
Percent		60	46	36	31	21	14	14	13	11	8							

*Lost contact

from onset of therapy was 33.0, which is slightly less than the survival rate of 33.8 in the entire 265 cases of Slaughter and Craver. These cases were all followed for periods of longer than 5 years, while our series includes some living cases who have been followed only 3 years. The 5-year survival rate is 16.4%, a considerable improvement over the series of Slaughter and Craver. (Table VI).

An estimate of the duration from the time of onset was made in 173 cases in whom the time of onset could be determined. The 5-year survival rate in this group is approximately 3 times as great in this group as in a series of untreated cases reported by Minot.[37] (Table VII). The interval between the time of onset and the time of the first treatment in those cases was 15.5 months.

Of 5 cases having a survival of more than 10 years, 4 cases are still living, the longest period of survival being 16 years. Still others are living 11, 13, and 14 years after the first treatment. The patient surviving 16 years had enlarged nodes in the cervical and axillary region which were treated in August, 1929. The patient has had no recurrence since that time and remains well. The lesions were apparently localized and were treated adequately with good results.

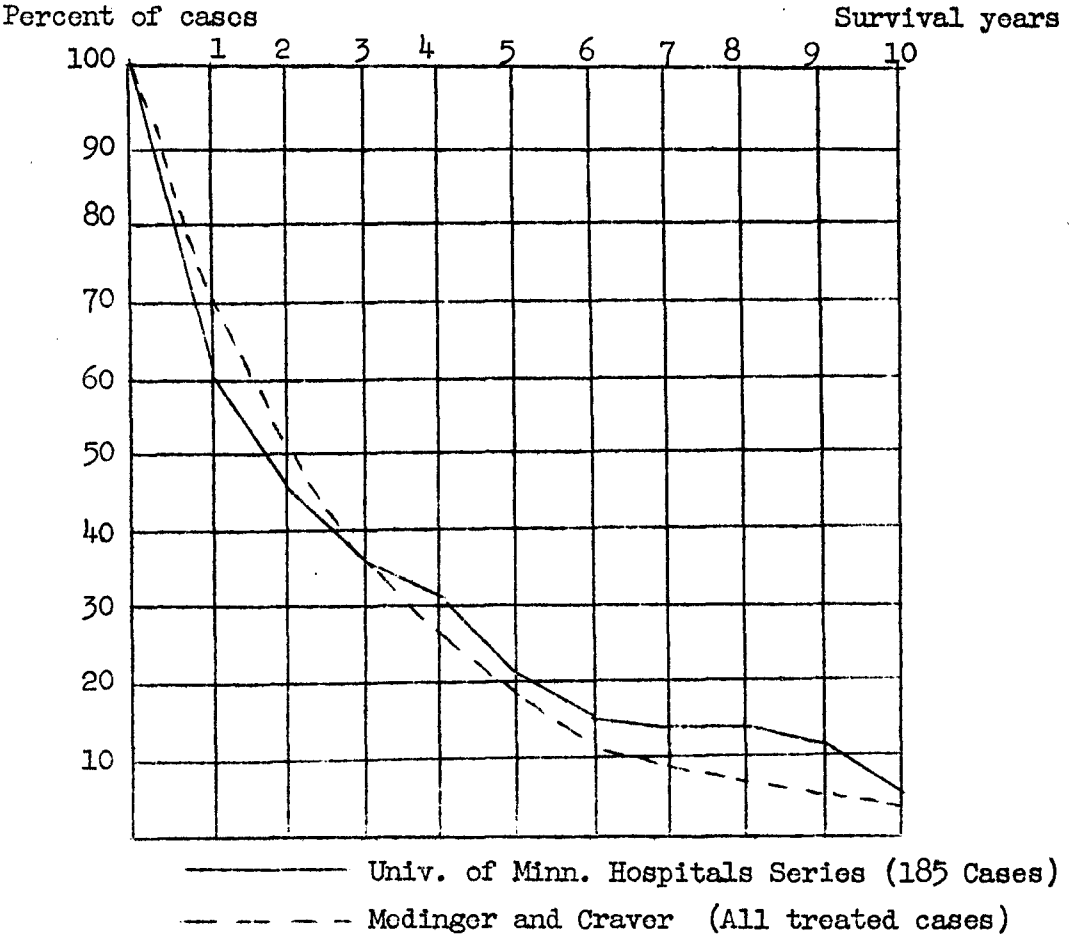
The case surviving for 14 years was given therapy in 1931 to the axilla, abdomen, mediastinum and spleen at the age of 12. This patient has had no recurrence until the end of December 1945. A mass developed in the cervical region in July 1945 and clinically was presumed to be recurrent Hodgkin's. After removal, however, microscopic examination revealed the characteristic structure of neurofibroma.

Cases Reported

Patient S. T. Female, aged 28, was admitted to the hospital in September, 1932 with a history of enlargement of the cervical nodes bilaterally, over the

Table VI

HODGKIN'S DISEASE
Survival Rates after Treatment



previous 18 months. Dyspnea of mild degree had been present about 2 months. Biopsy of the cervical nodes revealed the characteristic structure of Hodgkin's Disease, includine Dorothy Reed cells. An x-ray film of the chest demonstrated a mass in the upper mediastinum. The cervical nodes and mediastinum were treated with good response.

In February 1937, a mass developed over the sternum in the soft tissues on the right. The mass was firm, painless and measured 5 x 6 x 3 cms. The mass was treated with good response and completely subsided within 2 months.

In October 1939 a mass appeared below the left clavicle and an additional small mass in the right hilum. Both lesions were treated with satisfactory results.

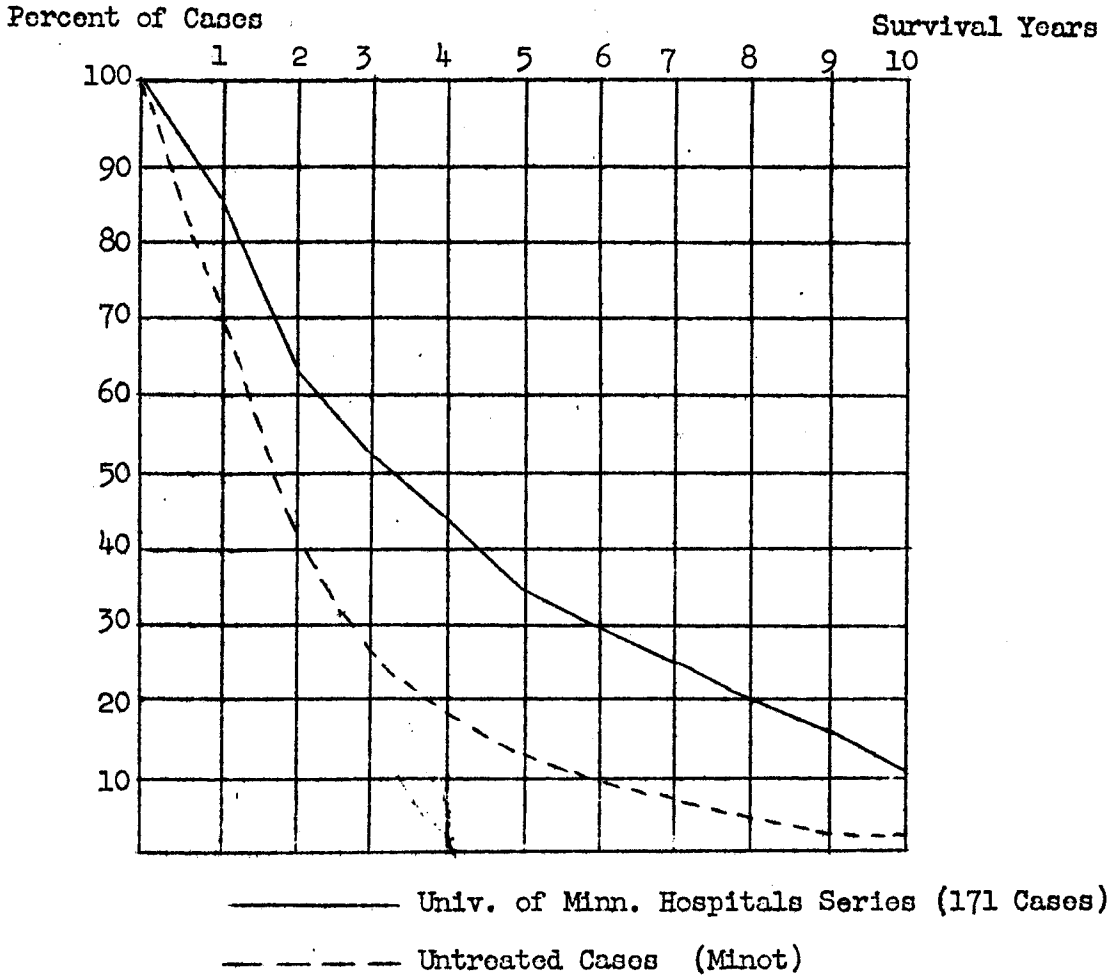
In May, 1941, inguinal nodes on the right were treated. In August 1941, pain of rather severe degree occurred in the lumbosacral region. X-ray examination revealed partial destruction of the body of lumbar 4. This area was treated with the usual dosage, producing partial relief from pain. In the meantime, a large hard mass developed in the left mid-abdomen, probably representing enlarged retroperitoneal nodes. After therapy to this region, the mass entirely disappeared.

Patient's health was quite good from November 1941 until August 1942, when she developed mild pain in the left flank. Pain continued until a visit to clinic in March 1943. A film of the lumbar spine showed partial destruction of the body of the first lumbar vertebra

Table VII

HODGKIN'S DISEASE

Survival Rate after Onset



and 12th rib on the left. Patient was treated in this area with considerable relief of pain.

Re-examination of the chest in May 1944 revealed an infiltrative lesion in the right base. Intensive therapy was given to this region with good results.

In March 1945, on re-admission, severe back pain in upper lumbar region with radiation of pain anteriorly was described. X-ray examination revealed further destruction of the 12th rib on the left and 1st lumbar vertebra, with an osteoblastic lesion in the body of the first lumbar vertebra which was a new lesion. On the 6th day after therapy, patient said she had complete relief of pain. She has remained well since that time. It is now over 13 years since the first treatment was given and multiple areas have been treated.

Summary and Conclusions

A method of irradiation therapy has been developed at this clinic, which we believe is very efficient in the treatment of lymphoblastomas. A series of 185 cases of Hodgkin's Disease proven by biopsy has been reviewed.

The method of therapy is considerably more intensive than for most series reported. A full course of therapy should be applied to each area of involvement, the dosage varying between 1000 and 2000 tissue roentgens over a

period of 14 days. Large masses should be treated more intensively and the group of enlarged nodes causing the greatest distress should be treated first. Prophylactic irradiation, in our opinion, is contraindicated.

The 5-year survival rate from the time of treatment in our cases was 21% and the 10-year, 8%, a high average when compared with other series. Other statistics have also been presented, demonstrating the marked increase in survival rate from the time of onset of symptoms in the treated cases when compared with a series of untreated cases reported by Minot in 1926.

The unpredictable nature of Hodgkin's Disease is recognized and claim for cures cannot be made. We believe our method of therapy, however, has increased the survival rate very substantially.

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III. GOSSIP

In two more days the world will celebrate the feast of St. Patrick, the patron saint of Ireland, one of the few national heroes who is so honored. St. Patrick while still a young man was brought to Ireland as a slave. He hailed from Brittainy and his ancestry is in doubt; many races have tried to claim him and only recently I saw where the Baptists, Presbyterians, Methodists, and Jews had advanced "proof" that he belonged to them. It was said of him that in captivity he learned to like Ireland and the Irish so well that he resolved to return after his release and become one of them. He took holy orders in the interval and returned to evangelize the people. Contrary to popular belief, the Irish were not all pagans before the time of St. Patrick. Apparently he attracted followers with ease, as before long his band was reported in various parts of Ireland. The pagan feast days arrived when it was forbidden to build public fires in honor of the gods unless certain of the chief priests started them. St. Patrick and his followers selected a hill opposite the place in which the "official" fires were to be lighted. They started their own in defiance of the authorities and then marched down to meet them. Legendary tales of the passage of the group through hostile territory are many, but eventually they reached the great hall itself where St. Patrick confounded the chief priests with his logic. This moral victory was only one of many which followed. The gentle soul who had been a sheep herder became a militant leader for Christianity. Two things characterized him, his human qualities and his saintly attributes. Before he had finished his life span, he had converted nearly all Ireland, established great churches, convents, and schools. Under his patronage, the country flourished and there was great prosperity and happiness. When he died, the Irish held the longest waque in their history, and when he was buried, every Irishman mourned. He found the hospitality of the people much to his liking, and even today the good hearted Irish are known throughout the world for their deeds of kindness. He gave their acts of charity a real meaning in their religion and to this day no matter where they are the Irish stop on the 17th of March to thank God for sending this wonderful man to them. Following St. Patrick, a great woman came into power, St. Bridgid. She it was who continued his educational policies and good works and obtained for women a position which they had not hitherto enjoyed. They inherited property and enjoyed many of the privileges they have today. They apparently did as they please and their husband liked it, for it was recorded of them that they painted their fingernails as do our ladies. Their dress was such that it emphasized their modesty as well as their good qualities. Once a year they had special affairs just for women in which they could do as they please. It sounds much like the St. Paul carnival, as they went around masked. This particular entertainment seems to be an old custom. Although legend give St. Patrick credit for driving snakes from Ireland, historians believe that there were few snakes in his time. I might add that apparently one particular variety of snake was left, and around him was told a most unhappy tale, i.e. that he struck his head up every morning looking for company or for a fight and found none. The Irish have had many plagues in their day. I am a product of the potato famine when my people were driven from the land through starvation. For many years the Danes were pests until soundly defeated by my great ancestor Brian Barou, the King of Munster, in one of histories most famous battles. In recent years, the British yoke has rested lightly on the land, and in World War II, although Ireland was not officially in the conflict, she sent many of her sons into battle to help our cause. Irish history is full of legend, heros, scoundrels, fights and celebrations. The most unpredictable of all people, they enjoy most of all speaking in riddles which no one but themselves can understand. The Irish Health Officer, who made out a report on an epidemic of pneumonia in which strong men died, told his British superior, "that men had died that year who had never died before". On St. Patrick's Day, everyone joins with the Irish in celebrating and the pious wish that St. Patrick's Day will continue to be a permanent day of jollification for the human race. At our house we celebrate the birth of St. Patrick himself as well as our son, Patrick James, who was born on this day, 8 years ago.