Roentgen Treatment for Hodgkin's Disease and Lymphosarcoma of the Chest

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Fifty years ago, Roentgen announced to the world his discovery of peculiar rays which had the property of passing through substances of low atomic weight. Not knowing what these rays were, he called them "X-rays". This discovery caused a tremendous sensation, and within a few months the new rays were already being applied to the examination of fractures and dislocations of bones, to find foreign bodies and to determine the possible influence of the rays on certain pathologic conditions. Now, after half a century, what does one find? Every hospital and clinic has a more or less important department of roentgenology, and every practicing physician must make use of Roentgen's rays for diagnosis and for treatment. For a physician to practice medicine without the help of these rays would now seem an unbelievable anachronism and would label him an old fogey.

Whenever treatment with roentgen rays is mentioned, lay persons as well as many physicians immediately assume that treatment of malignant tumors is meant. This is far from true. At the present time and for some years roentgen rays have been used increasingly for the treatment not only of tumors but also of inflammatory conditions, acute and chronic. In several previous communications I have dealt with the treatment of inflammatory lesions. In this paper I shall attempt to set forth basic ideas about the treatment of malignant neoplasms, especially as it applies to neoplasms of the chest. But in order to understand how this kind of treatment acts on tumors it is important to know certain fundamental principles which are based on a large body of experimental evidence as well as on extended clinical observations.

SENSITIVENESS OF NORMAL CELLS

Each variety of cell in the body is specifically sensitive to roentgen rays. Certain varieties of cells are extremely sensitive and are destroyed or injured by small doses; other varieties are resistant and can tolerate large doses with apparent impunity. This does not imply that a given dose of rays can destroy all cells of a given variety in the irradiated territory, because the sensitivity of any kind of cell varies somewhat from cell to cell. It

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would be more accurate to say, therefore, that each variety of cell has a specific range of sensitiveness.

When cells of a given kind are exposed to a certain dose of radiation, some are destroyed, some are injured but regenerate later, and some do not show any deleterious effect. This variation in the susceptibility of different cells of the same kind is probably due to the metabolic stage of the cells and perhaps to other unknown factors. Whatever the main reason for variation in the radiosensitivity of different cells of the same variety may be, this does not affect the fundamental law of the specific sensitiveness of different varieties of cells, a law based on innumerable experiments on animals and substantiated by extensive clinical observation.

According to present knowledge, cells may be classified, in the order of the degree of their sensitiveness, as follows:

Lymphoid cells (lymphocytes in the spleen, lymph nodes, intestinal lymph follicles, circulating blood, bone marrow, thymus, tonsil and other structures in which these cells may be present).

Polymorphonuclear leukocytes and eosinophils in the blood or tissues.

Epithelial cells: (1) basal epithelium of certain secretory glands, especially the salivary glands; (2) basal epithelium (spermatogonial cells) of the testis and follicular epithelium of the ovary; (3) basal epithelium of the skin, mucous membranes and certain organs, such as the stomach and small intestine; (4) alveolar epithelium of the lungs and epithelium of bile ducts (liver) and (5) epithelium of tubules of the kidneys.

Endothelial cells of blood vessels, pleura and peritoneum.

Connective tissue cells.

Muscle cells.

Although the difference in susceptibility between the most sensitive and the least sensitive varieties of cells is considerable, no cell in the body is wholly invulnerable to radiation; all cells, whatever their variety, may be destroyed or injured if exposed to a sufficiently large dose of rays, especially if doses within the therapeutic range are disregarded. The experiments of Bergonié and Tribondeau and others have shown conclusively that the younger and the more active the cell, from a metabolic point of view, the more susceptible it is to the influence of the rays. Cells which naturally undergo rapid mitotic division and the life cycle of which, therefore, is comparatively short are most sensitive; and cells which have a long life cycle are relatively resistant to the rays. But the relation of the age of the cells to the relative sensitiveness is less important than the specific vulnerability of the different varieties of cells.
In order to give a clear idea of the effect of irradiation on cells, I shall describe the changes which can be observed in sensitive cells, such as lymphocytes, after exposure to roentgen rays.

The exceptional sensitiveness of lymphocytes was established by the early experiments of Heineke and has since been fully confirmed by Krause and Ziegler, Fromme, Jolly, Tsuzuki, Piepenborn, Warthin and many others. When the entire body of an animal is exposed to roentgen rays, the spleen, the mesenteric and other lymph nodes, the intestinal lymph follicles, the blood and bone marrow, the thymus in young animals and other collections of lymphoid tissue show a more or less marked destruction of lymphocytes, and the degree of destruction is proportional to the dose of rays and to the interval between irradiation and death. As the number of intact lymphocytes in the spleen and lymph nodes diminishes, the stroma becomes more prominent, and this feature may become so pronounced that the malpighian corpuscles or lymph follicles may largely disappear and may be recognized only by the blood vessels and by the concentric arrangement of the corpuscular or follicular stroma. Heineke found destruction of lymphocytes two hours after irradiation, but Warthin, who examined the lymphoid structures sooner after exposure to the rays, found unmistakable evidence of lymphocytic disintegration within fifteen minutes after irradiation.

The destruction of these cells is characterized by disorganization and fragmentation of the nuclear chromatin and by scattering of the fragments of chromatin between the remaining intact cells and in the spaces of the reticular stroma, where the fragments gather into clumps or balls. The extent and the duration of this destructive phase depend on the intensity of irradiation. It may continue from one to several days and may be accompanied by a progressive reduction in volume or atrophy of the affected lymphoid structures. Then the clumps or balls of degenerate chromatin are gradually taken up by some of the reticular cells, which assume a phagocytic property and swell as the amount of ingested chromatin debris increases. The phagocytic disposal of chromatin material from the destroyed cells may continue until the lymphocytes are largely destroyed, but a certain proportion of the cells appear to resist the action of the rays. Some hours or days later, the phagocytic reticular cells themselves begin to disappear. The chromatin debris ingested by the phagocytes apparently undergoes intracellular digestion, because the number and size of the ingested fragments diminish steadily. From seven days to three weeks after irradiation, more or less regeneration of lymphoid tissue may be observed.

Similar changes occur in other kinds of cells but, because they
are less sensitive, a larger dose of rays is required to produce an equivalent effect or, if the dose of rays is the same, fewer cells are affected and the effect is less pronounced. Also, the cellular changes induced by irradiation do not begin so soon after exposure and do not last so long. This difference increases as the relative sensitiveness of other kinds of cells decreases.

SENSITIVENESS OF MALIGNANT TUMORS

The sensitiveness of tumors to roentgen rays corresponds closely to that of the cells of which the tumors are chiefly composed. Thus, tumors derived from lymphoid cells or from the basal cells of the genital glands (testis or ovary), as well as from the embryonal epithelium of the kidney in children (Wilms' tumor), are extremely sensitive. Neoplasms arising from adult epithelium are only moderately sensitive and tumors derived from connective tissues are much more resistant. Like different varieties of normal cells, malignant tumors of different kinds can be classified according to their sensitiveness to roentgen rays. Elsewhere I have ventured to make such a classification, and those who may be interested will find the reference in the bibliography.

Knowledge of the comparative sensitiveness of different kinds of neoplasms often makes it possible to distinguish certain varieties of tumors from other varieties which are more or less sensitive, and this method can often furnish information of the greatest value and could be employed much more than it now is. Thus, in connection with intrathoracic tumors, exposure to roentgen rays almost always permits one to establish a clear distinction between Hodgkin's disease or lymphosarcoma and an aneurysm of the aorta, between these forms of lymphoblastoma and carcinoma of a bronchus, neurofibroma, fibrosarcoma, teratoma, or a desmoid tumor, or between lymphoblastoma and tuberculous adenitis. Moreover, when the action of roentgen rays on a tumor is correlated with the history, clinical features and physical findings, the diagnostic value of this therapeutic test can be extended considerably. Needless to say, the use of this test requires extended experience and, as will be explained later, the treatment must be arranged in a certain manner. Mere exposure to a roentgen tube in operation is not sufficient.

CLINICAL AND OTHER CONSIDERATIONS

Before considering roentgen treatment for these conditions, it would not be amiss, perhaps, to review a number of points which often have an important bearing on treatment.

In the average case, from a clinical as well as from a therapeutic point of view, these forms of lymphoblastoma are identical. By
this I mean that, in both of these conditions, the pathologic process can begin in the same region and can invade other groups of nodes in precisely the same manner and at the same rate. Clinically, in other words, there is no essential difference between them. From the standpoint of treatment, also, these conditions are influenced by a given dose of roentgen rays in the same manner and at the same average rate. In the past, some writers have claimed that lymphosarcoma is more sensitive to roentgen rays than Hodgkin's disease, and vice versa. This contention, I am convinced, has been based on limited experience. After having treated more than 5,000 patients during the past twenty-five years, I have been forced to conclude that, in the average case, these conditions are so nearly identical that one cannot be distinguished from the other, either clinically or therapeutically. To me they appear to be members of the same family.

Hodgkin's disease and lymphosarcoma are more common than earlier writers have led one to believe. This is probably because these conditions begin very insidiously; because, in the past, they were often mistaken for other conditions, such as tuberculous adenitis; and because, even now, in some cases the disease is not recognized until the pathologic process has reached a rather advanced stage. Another reason is that too much attention has been concentrated on the lymph nodes in the neck, armpits and groins. It is true that these conditions often begin in the cervical lymph nodes or in the nasopharynx or tonsil, but when any or all of these structures are involved, this does not necessarily mean that the process began there. In about an equal percentage of cases these conditions begin in the retro-abdominal lymph nodes, especially the para-aortic or iliac nodes, but sometimes the mesenteric nodes also are affected sooner or later.

As far as the lymph nodes in the chest are concerned, those in the mediastinum (right and left paratracheal nodes or tracheobronchial nodes, or both) are most commonly involved. However, Hodgkin's disease or lymphosarcoma begins in the mediastinal nodes much less commonly than it begins in the head, neck, or retro-abdominal nodes. In most cases, when the mediastinal nodes are invaded, the involvement of these nodes is secondary to similar, but earlier, involvement of lymph nodes in other regions.

An interesting, and sometimes an important, point to remember is that, when lymph nodes in the axilla are affected by these conditions, the mediastinal nodes also are usually involved, although in some cases involvement of these nodes cannot be demonstrated easily because the nodes have not become sufficiently large to project beyond the borders of the sternum and spinal column; and the reverse is often true, but the latter is less common than
the former. Similarly, when the inguinal nodes are affected, it can almost be taken for granted that the retro-abdominal (para-aortic, mesenteric or iliac) nodes also are involved. In 1939 I drew attention to these points, and since then Symmers (1944) has confirmed their validity by extended observations at necropsy.

By physical examination alone, as most physicians know, it is often difficult or impossible to recognize intrathoracic involvement in these conditions, and even when roentgenoscopy or roentgenography is employed, it may be impossible to distinguish Hodgkin's disease or lymphosarcoma from other neoplastic processes, such as carcinoma, neurofibroma, fibrosarcoma, teratoma, thymoma, or the so-called Pancoast tumor. This is especially true during the early stage, but it is often true at any stage. One reason for this difficulty is that different kinds of tumors in the chest can grow in such a way as to produce very similar roentgenologic signs. While, in most cases, Hodgkin's disease or lymphosarcoma involves nodes in both sides of the mediastinum and, consequently, produces a bilateral shadow which usually is nodular, lobular and more or less typical, it is not rare for these conditions to involve the nodes in one side much more than those in the other side; or even, as far as roentgenologic appearances go, the involvement may appear to be confined to the nodes in one side of this region. Sometimes, either in their original form or by some of the peculiar vagaries which may arise during their course, these forms of lymphoblastoma can simulate many other malignant neoplasms as well as some inflammatory conditions.

Involvement of thoracic wall: Hodgkin's disease or lymphosarcoma sometimes invades the chest wall, but usually, when this occurs, the involvement is secondary and not primary. Thus, in a few cases, a mass may slowly form in the subcutaneous tissues over the upper part of the sternum, usually at the level of the junction of the manubrium and the body of the bone. As a rule the greatest bulk of the mass lies slightly to one side or the other of the median line. When left untreated, the tumor gradually increases until it forms a mass the size of a fist, or even of two fists. When a surgeon ventures to explore such a tumor, he usually finds that it extends, in depth, through the inner part of one or more intercostal spaces adjacent to the sternum and is part of a similar process in the anterior mediastinum. In other words, it is an outward extension of a malignant lymphoid process in the anterior mediastinal nodes. Seldom are the ribs or sternum themselves affected, but occasionally the sternum may be eroded by the slowly increasing pressure of enlarging mediastinal nodes.

In a few cases, when the malignant process has advanced considerably, nodules appear in the skin or immediately beneath it;
nODULES OF THIS KIND MAY DEVELOP IN ANY PART OF THE BODY. AT FIRST THE COLOR OF THE OVERLYING SKIN IS NORMAL BUT, AS THE NODULAR INFILTRATION PROGRESSES, THE SKIN OVER THE NODULES SLOWLY ASSUMES A REDDISH HUE, AND LATER THIS REDDISH HUE TURNS TO A DULL, BEEF-RED COLOR. SOMETIMES ONLY A FEW NODULES MAY BE SCATTERED IRREGULARLY, BUT SOMETIMES THE TRUNK OR EXTREMITIES MAY BE STUDDED WITH THEM.


INTRATHORACIC INVOLVEMENT: MOST COMMONLY, WHEN THE INTRA-THORACIC STRUCTURES ARE INVADEN BY THESE FORMS OF LYMPHOBLASTOMA, THE CONDITION BEGINS IN THE MEDIASTINAL NODES, BUT ONLY IN A SMALL PROPORTION OF CASES DOES INVOLVEMENT OF THESE NODES REPRESENT THE PRIMARY LESION; IN MOST CASES IT REPRESENTS EXTENSION FROM THE CERVICAL OR RETRO-ABDOMINAL NODES. IN A FEW CASES, HOWEVER, HODGKIN'S DISEASE OR LYMPHOSARCOMA, WHICH MAY HAVE BEEN ACTIVE IN THE ABDOMINAL PARA-AORTIC NODES FOR A LONG TIME, MAY EXTEND THROUGH THE DIAPHRAGM AND MAY INVADE THE PLEURAL LYMPHATICS OVER THE THORACIC SURFACE OF THE DIAPHRAGM.

INVOLVEMENT OF MEDIASTINAL NODES BEGINS IN ONE NODE AND GRADUALLY EXTENDS TO OTHER NODES, AND THE NUMBER AND SIZE OF THE AFFECTED NODES TENDS SLOWLY TO INCREASE. IN THE MAJORIT OF CASES THE NODES IN THE UPPER HALF OF THE MEDIASTINUM ARE MAINLY AFFECTED, BUT IN A SMALL NUMBER OF CASES THE MAJOR INVOLVEMENT MAY AFFECT NODES IN THE UPPER PART OF THIS REGION, AT OR JUST BELOW THE INLET OF THE THORAX, OR IT MAY PRINCIPALLY AFFECT NODES IN THE LOWER HALF OF THE MEDIASTINUM. USUALLY, AS THE AFFECTED NODES CONTINUE TO ENLARGE, THEY PROJECT LATERALLY TOWARD AND INTO THE
Fig. 1: Roentgenograms of the chest in case 1.

Fig. 1a: Roentgenogram made on December 3, 1941. It shows an enormous tumor occupying the upper two thirds of the space ordinarily occupied by the right lung. Clinically or roentgenologically, it would be impossible to know which of several kinds of tumor this could be.—

Fig. 1b: Roentgenogram made on December 22, 1941, three weeks after a course of roentgen treatment. It shows marked regression of the tumor. This rapid regression clearly indicated that the growth was a manifestation of lymphoblastoma (Hodgkin's disease or lymphosarcoma) and that it could not be a carcinoma, fibrosarcoma, neurofibroma, dermoid, teratoma or Pancoast tumor.—

Fig. 1c: Roentgenogram made on December 26, 1941, without further treatment. It shows still greater regression of the tumor and this strongly confirms the previous conclusion.—

Fig. 1d: Roentgenogram made on January 12, 1942, without additional treatment. It shows marked regression of the tumor which was then only a small fraction of its original size. A tumor derived from epithelial, connective or nerve tissue, or a teratoma, could never be influenced so rapidly and so much by roentgen rays. In this case, the rate of regression was somewhat more rapid than in the average case of mediastinal lymphoblastoma.
hilus of the lungs, but sometimes the nodes principally involved are in the anterior part of the mediastinum, and they may or may not be visible in roentgenograms. It is important to remember that, for lymph nodes to project laterally beyond the composite shadow cast by the sternum and spinal column, they must be rather large or numerous. Sometimes mediastinal nodes that are not large enough to be seen in roentgenograms may nevertheless cause symptoms, such as cough, or pain around one or both shoulders or in one or both of the upper extremities. Roentgen treatment directed toward the mediastinum through two large anterior and two corresponding posterior fields often causes these symptoms to abate rapidly or to disappear.

When Hodgkin’s disease or lymphosarcoma involves the mediastinal nodes a roentgenogram of the thorax usually reveals a bilateral and roughly parallel widening of the shadow projected by the mediastinal structures, which extends from the suprasternal notch downward to the cardiac shadow which it overlaps more or less. This shadow is cast by affected right and left paratracheal nodes. In many cases the tracheobronchial nodes also are involved more or less extensively, and they cast an irregularly nodular shadow which projects outward beyond the vertical and parallel shadow produced by the paratracheal nodes. But in other cases roentgenography may not reveal this “typical” appearance, but may disclose a small or large tumor apparently confined in one side of the chest. Often this is situated in the upper part of the chest, where it may occupy space ordinarily taken by a portion of the upper lobe of one lung, or by all of it (Fig. 1). The tumor may be round and sharply circumscribed; it may be irregular and may have ill-defined and feathery margins, or it may have the form of a bird’s wing, and its appearance may suggest extension upward and outward from the mediastinum. Certainly there is nothing characteristic about it and the tumor could as readily be carcinoma, fibrosarcoma or some other malignant growth, as Hodgkin’s disease or lymphosarcoma. Besides the foregoing, other unusual forms may be observed in different cases.

Sometimes, besides more or less definite involvement of mediastinal nodes, an abnormal shadow may extend outward between two lobes of one lung as far as the periphery; this may be caused by infiltration of the interlobar pleura and, if so, roentgen treatment should cause it as well as the affected nodes of the mediastinum to diminish or disappear.

Occasionally, the nodes chiefly involved are high in the mediastinum (Fig. 2) and the symptoms may include not only dyspnea, with or without dysphagia, but also a brassy cough, hoarseness from involvement of one or both recurrent laryngeal nerves, puf-
finess and cyanosis of the neck and face and prominence of the superficial veins due to venous obstruction at or near the inlet of the thorax. Pressure may also be exerted on the trachea which may be displaced more or less, and this may be accompanied by increasing dyspnea and cough and by an expression of anxiety. The cervical nodes also may be abnormally large but, owing to the puffiness and engorgement, they may be difficult to perceive with certainty. A physician who is "thyroid conscious" may think that the roentgenogram suggests substernal extension of the thyroid (Fig. 3), but well-planned treatment, if given before these disturbances have been present too long, can often relieve them, at least for a time. For some obscure reason, when the lymph nodes in this part of the mediastinum are mainly affected, they are not influenced as rapidly by treatment as when the greatest involvement affects nodes lower in the mediastinum, and the degree of regression induced by treatment is often much less. Moreover, at necropsy, the affected nodes in this region often

Figure 2: Roentgenograms of the chest in case 2.

Fig. 1a: Roentgenogram made on January 31, 1945. It shows some widening of the upper part of the mediastinal shadow and an unusual lesion in the posterior peripheral portion of the parenchyma of the right lung, at the level of the sixth and seventh ribs. This lesion was thought to be tuberculosis. The patient's head, face and neck had become engorged (puffy) and cyanotic, the superficial veins of the anterior wall of the chest and abdomen had become prominent, he had become progressively weaker and his weight had diminished 14 pounds (6.4 kg.) in six weeks. Enlarged lymph nodes were present in both sides of the neck and in both armpits.—Fig. 1b: Roentgenogram made on March 12, 1945, after a single course of roentgen treatment. It shows considerable reduction in the width of the mediastinal shadow and in the area of interlobar infiltration in the right lung. The venous engorgement and cyanosis of the head, face and neck had disappeared and the patient felt and appeared to be much better.
contain an unusual proportion of connective tissue cells. It is not clear why, under these circumstances, the nodes should contain an exceptional proportion of connective tissue cells. A possible explanation might be the passive congestion resulting from pressure on the veins, but this is only conjecture.

In some cases of mediastinal lymphoblastoma, roentgenograms of the chest show little, if any, widening of the mediastinal shadow, and yet the symptoms suggest more or less definite involvement of the tracheobronchial nodes in and around the angle of the tracheal bifurcation. The reason the roentgenograms do not show lateral projection beyond the edges of the composite shadow cast by the sternum and spinal column may be that the affected lymph nodes have an anteroposterior disposition. In any event, exposure to roentgen rays through two anterior and two posterior fields, with the four beams of rays converging sharply on the mediastinal structures, is often as effective as in cases in which the anatomic disposition of the affected nodes is more orthodox.

Sometimes, a patient complains of pain in the chest or around one or both shoulders, or the pain may extend to one or both of the upper extremities. Occasionally, the pain may be confined to the extremities, and the patient may not have pain in the chest. Roentgenograms may show obvious or even marked involvement of mediastinal nodes, but in some instances evidence of mediastinal involvement may be slight or actually uncertain. Under these circumstances, it is important to exclude, by careful examination, the possibility that the pain may be due to pressure irritation or actual infiltration of branches of the brachial plexus on one or both sides by lymphoblastoma affecting some of the cervical nodes or by nodes in the upper part of the axillary (infraclavicular) space. When this possibility can be excluded, the treatment should be directed toward the mediastinum, as I have already suggested.

In lymphoblastoma, pleural effusion may be caused by obstruction of the inferior vena cava by enlarged nodes in the lower part of the mediastinum; because the adenopathy is concealed by the cardiac shadow, it may not be visible in ordinary roentgenograms, but its presence may be revealed by roentgenograms made by the method of Bucky. The effusion also may be due to infiltration of the pleura. In cases of this kind, effective irradiation requires that the fields be large enough to include the lower two thirds of the mediastinum as well as the entire diaphragm. Involvement of this kind, however, usually occurs only when the pathologic process has reached a relatively advanced stage, and prolonged improvement can hardly be expected under these circumstances.
Rarely, Hodgkin’s disease or lymphosarcoma may infiltrate the lungs in what approximates a miliary manner or it may have the appearance of a falling, wet snow. That is, the infiltration is scattered more or less uniformly throughout the lungs and may readily be confused with metastasis from carcinoma or with some forms of tuberculosis. Infiltration of this kind indicates that lymphoblastoma has invaded most or all of the small aggregations of lymphoid cells situated at the junction of the smaller branches of the bronchi. This also is a relatively late complication. Nevertheless, thorough treatment may result in pronounced improvement, the duration of which may vary greatly in different cases.

In a small proportion of cases, Hodgkin’s disease or lymphosarcoma, instead of affecting chiefly nodes in the anterior or middle part of the mediastinum, involves mainly nodes in the posterior mediastinum, and as the affected nodes continue to enlarge, one of two things may occur: either the enlarging nodes cause pressure on adjacent vertebrae and destructive erosion of some of these bones occurs, or the pathologic process may infiltrate an intervertebral space and thence may extend into the spinal canal, where it may even invade the spinal cord. When roentgenograms of the spinal column reveal destructive changes in one or more vertebrae, this is often assumed to represent metastasis from carcinoma, even when a primary tumor in some epithelial structure cannot be found, when the patient is rather young to be afflicted with carcinoma, when his general condition is altogether too good considering the character and duration of

Figure 3: Roentgenograms of thorax in case 3.

Fig. 3a: Roentgenogram made on July 31, 1944. It shows an enormous intrathoracic tumor with bilateral involvement and with an outward projection toward the periphery on the right side. Besides the intrathoracic tumor, the neck was enormously and diffusely enlarged; the enlargement was smooth and soft and gave the impression that a large volume of air had been injected beneath the skin. This enlargement of the neck was not caused by air, but by distention and engorgement of veins from pressure on the great vessels just below the thoracic inlet and by enlargement of cervical lymph nodes.—Fig. 3b: Roentgenogram made on November 14, 1944, after two courses of roentgen treatment, part of which was directed toward the chest and part of it toward the neck. During and after the first course of treatment, the size of the intrathoracic tumor as well as the enlargement of the neck diminished steadily. The patient’s condition improved rapidly, and the malignant process continued to regress after the second and third courses of treatment. By that time the enlargement of the neck as well as the cough and dyspnea had disappeared, the patient’s weight had increased six pounds (2.7 kg.) and she looked much better.—Fig. 3c: Roentgenogram made on January 22, 1945, after three courses of roentgen treatment. It shows marked, but still incomplete, regression of the intrathoracic tumor.—Fig. 3d: Roentgenogram made on April 4, 1945. It shows still greater regression, but on the right side at the level of the hilus there is evidence of fresh enlargement of lymph nodes. On this account a fourth course of treatment was given.—Fig. 3e: Roentgenogram made on May 21, 1945. It shows still greater regression of the intrathoracic tumor. The patient was entirely free from symptoms and may remain so for an indefinite period.
his illness and when enlarged nodes in other regions would hardly
be consistent with a diagnosis of carcinoma or epithelioma.

TREATMENT

When a thoracic or intrathoracic tumor is suspected of rep-
representing Hodgkin's disease or lymphosarcoma, this suspicion can
often be confirmed or excluded. Since tumors of this kind are
largely composed of hyperplastic lymphoid cells, they are usually
very sensitive to roentgen rays, a sufficient dose of which causes
the tumor or tumors to retrogress rapidly. The rate and degree
of regression vary to some extent in different cases, and this
variation is undoubtedly related to histopathologic differences in
the affected lymphoid structures. Nevertheless, in the majority
of cases a lymphoblastomatous tumor in the mediastinum or chest
can be expected to shrink from 30 to 100 per cent within three
or four weeks after a well-planned course of treatment. Naturally,
the degree of regression in each case depends on the size of the
enlarged nodes before treatment.

In some cases the first course of treatment may not cause the
tumor to diminish more than 25 per cent; as I have already men-
tioned, this may be due to the presence in the tumor of an excep-
tional proportion of connective tissue, which prevents the growth
from being influenced as much as it would be otherwise. Another
element which may diminish the effect of the rays is the assos-
ciation in the affected mediastinal nodes of Hodgkin's disease
or lymphosarcoma and tuberculosis, but this association occurs
only in a small percentage of cases. A third factor which may
prevent enlarged lymph nodes in the mediastinum or elsewhere
from being influenced by the rays as much as would usually be
expected is related to the stage of the pathologic process. When
the malignant process has reached an advanced stage or has
entered the terminal phase, when several groups of nodes in dif-
ferent parts of the body, and especially the retro-abdominal (para-
aortic, mesenteric or iliac) and mediastinal nodes, are extensively
involved, and when the patient's general condition has deterio-
rated considerably, the influence of the rays may diminish and
the affected lymphoid structures may respond less than usual or
may not respond at all. This varies more or less in different cases,
but the general rule holds.

Sometimes a patient may appear to be quite ill and may have
severe dyspnea or orthopnea, severe cough, a rapid pulse, and one
or both pleural cavities may contain a considerable amount of
fluid; yet well-planned treatment may still be accompanied and
followed by rapid and marked improvement. This is especially
true when the nodes in other regions are not greatly involved,
but it may be true even when they are; under these circumstances, however, the degree of improvement is not likely to be so great or to last so long.

Anatomic arrangement of the treatment: Whether the treatment is given to distinguish one variety of tumor from another variety, or whether it is given purely for its therapeutic effect, it should be arranged in the same manner, and this arrangement depends mainly on the situation of the affected structures and on the predominating symptoms.

In the majority of cases in which the mediastinal lymph nodes are involved, treatment should best be arranged through two large anterior and two corresponding posterior fields, as shown in figure 4. How large the fields should be depends on the size of the patient. Vertically the fields should extend from the level of the suprasternal notch down to the level of the ensiform cartilage. Horizontally, or transversely, they should extend from the median line to the anterior axillary line. The four beams of rays should be directed toward the central part of the chest at an angle of 30 or 40 degrees. When, as is commonly done, treatment is arranged through only two fields (one anterior and one posterior), its effect is much less favorable. This is not surprising, because, with the former arrangement (two anterior and two posterior fields), the quantity of rays reaching the mediastinal structures and the inner portion of the lungs is twice as great (or nearly so) as when treatment is given through only two fields (one anterior and one posterior).

When the nodes principally affected are in the upper part of

Fig. 4: Arrangement of fields for treatment of the mediastinum and lungs. The arrows indicate that the four beams should be directed inward more or less according to whether the treatment is directed only toward the mediastinal structures and inner part of the lungs or is directed toward the mediastinum and greater part of the lungs.
the chest, just below or in the inlet of the thorax, and when the symptoms and physical signs indicate pressure on the superior vena cava and innominate veins, whether or not the deep cervical nodes also are involved, treatment should be directed toward the mediastinum in the manner which has been described, but it should also be directed toward the thoracic inlet and lower half of the neck through two additional fields, as shown in figure

Fig. 5: Arrangement of fields when, besides the mediastinum, the inlet of the thorax and lower part of the neck also should be treated. The arrows indicate that the two beams of rays should be directed inward and downward toward the thoracic inlet.

Fig. 6: Arrangement of fields when, besides the mediastinum and central part of the lungs, treatment should also be directed toward the upper half or two thirds of the abdomen. The arrows indicate that all the beams of rays should be directed inward and backward (anterior fields) or inward and forward (posterior fields).
5. And when, besides involvement of mediastinal nodes or lungs, the retro-abdominal nodes also are affected, additional treatment should be directed either toward the upper half of the abdomen through two anterior and two posterior fields (Fig. 6) or toward the entire abdomen through four anterior and two of four posterior fields (Fig. 7), according to circumstances.

**Quality of the rays:** For some years it has been a sort of fashion to treat all kinds of malignant tumors with rays generated at 200, 400, 600 or even 1,000 kilovolts and filtered through 0.5, 0.75, 1.0 or 2.0 millimeters of copper, or even more, and to administer treatment by the so-called fractional method, with as large a total dose as possible. This idea sprang from the results of experiments on animals performed by Regaud and his co-workers, and by others; these experiments had shown that, when living tissue is exposed to roentgen rays in small, fractional doses, a much larger total dose can be given without producing serious damage than when the same tissue is exposed to a single dose at one time. The experiments of Wood and Prime in this country had shown that, in order to stop the growth of epithelial tumors, a total dose of rays from five to eight times the limit of tolerance of any given area of skin is required. Since the only safe way in which such a dose can be given is by dividing it into small fractions which are given twice or once a day, or every other day, this method of treating malignant tumors has been widely adopted and is applied almost indiscriminately to tumors of all kinds.

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**Fig. 7:** Arrangement of fields when the mediastinal, retro-abdominal and iliac lymph nodes must all be treated.
Other factors which have influenced many to "standardize" treatment in this manner have been the trend toward greater and greater "depth doses" obtained by increasing voltage and filtration and the conception that the effect of the rays does not vary with the voltage, but only with the quantity (number of roentgens) delivered to the tumor.

But methods which may be entirely rational when employed in the treatment of epithelial neoplasms or of tumors which have an equal or greater resistance to roentgen rays may not be so effective when applied to tumors which are much more sensitive to the rays. I have already pointed out how extremely sensitive are lymphocytes, or lymphoid cells, in comparison with epithelial cells; this difference is so great that many physicians find it difficult to believe. A dose of 10 roentgens is sufficient to destroy a small proportion of lymphoid cells in a lymph node, and a dose of 100 roentgens causes greater destruction of these cells, whereas about 600 roentgens of rays generated at the same voltage are required to destroy a perceptible number of epithelial cells in the skin.

For many years, as far as treatment of Hodgkin's disease or lymphosarcoma is concerned, I have observed that rays generated at 200 kilovolts or more and filtered through 0.5, 0.75, 1.0 or 2.0 millimeters of copper (or through an equivalent thickness of zinc) are not as effective as is a corresponding dose of rays generated at 130 or 140 kilovolts and filtered through 4.0 or 6.0 millimeters of aluminum. Some years ago, comparative tests of treatment with rays produced at these two ranges of voltage gave results which were clearly in favor of the lower voltage, and subsequent experience has amply confirmed the results of those tests. How can this difference be explained? The only explanation I can think of is that, when the rays are generated at 200 kilovolts or more, a considerable proportion of the rays pass through the exposed region without being absorbed and, therefore, without producing any cellular effects, but when the rays are generated at moderate voltage (130 to 140 kilovolts), a larger proportion of them are absorbed by the cells in the exposed territory. In my experience, treatment at moderate voltage is more effective, both immediately and for the long run, than treatment at high voltage.

Quantity of rays: Because, in epithelial and other resistant tumors, effective destruction of the malignant cells requires the largest dose of rays which can be given with safety, it is widely assumed that the same is true of all malignant processes. When lymphoblastoma is limited to a single region, and especially when it is confined to a small cluster of nodes, the hope of permanent cure may reasonably be entertained and a complete result can
rarely be achieved, but this is never true when the pathologic process involves the mediastinal nodes or other thoracic structures. Under these circumstances, complete and permanent regression of the lymphoblastomatous lesions is practically out of the question; the most that can be expected is marked regression and prolonged remission. In most cases, therefore, the aim should be to obtain maximal improvement and to maintain this improvement as long as possible. This can seldom be achieved with rays generated at high voltage, with maximal doses given by the fractional method. To follow this course may yield excellent initial results, and treatment may be repeated at long intervals once or twice at most, but when the pathologic process again becomes active, as it inevitably does, further treatment is impossible or, if it is undertaken, it has little, if any, effect and the patient no longer can obtain relief.

Sometimes treatment is given with rays generated at high voltage (200 kilovolts or more), but the surface dose given to each field does not exceed 600 roentgens, and this dose is divided into daily fractions of 100 or 200 roentgens. This is more effective than the fractional method with a maximal total dose, but a still more effective method is to employ rays generated at 130 or 140 kilovolts and filtered through 6 millimeters of aluminum, and to give to each field a surface dose of 550 roentgens at one time (on one day); when the patient cannot tolerate 550 roentgens in one session, half of this dose may be given on one day and half the next. Then the other fields should be similarly treated in rotation and as rapidly as the patient's tolerance allows. Thus, when the chest alone requires treatment, the four fields (each receiving 550 roentgens) can usually be irradiated in four successive days. Irradiation of the chest seldom causes marked radiation sickness. But when, besides the chest, the upper half of the abdomen or the entire abdomen must also be treated, the course of treatment consumes much more time and may require from eight to sixteen days, according to the patient's tolerance.

As I have already indicated, a single course of treatment such as has been outlined, when given to a patient who had never been treated before, may be expected to cause the affected lymph nodes to retrogress from 25 to 100 per cent in three weeks. But even when the treatment is followed by what may appear to be 100 per cent regression, it is almost always wise to give a second course of similar treatment three weeks later, provided the number of leukocytes in the blood has not diminished too much. The reason for repeating the treatment is that it causes the regression and improvement to last much longer than would be likely to happen after a single course of treatment. In cases in which the initial
involvement is rather marked it is often wise to give three courses of treatment, but the interval between the second and third courses may be increased to five or six weeks.

Subsequently the patient should be examined at regular intervals; for the first year this may be once in three months, but, when signs of fresh activity of the pathologic process in the lymph nodes do not appear during this period, the intervals may be increased to four or even six months. Sometimes the improvement may continue for several weeks or several months, and sometimes it may continue for two, three or more years; this varies greatly in different cases and depends mainly on whether the patient is afflicted with Hodgkin’s disease or lymphosarcoma in a relatively acute or subacute form, or whether the process has a relatively chronic form. If, when the patient is first seen and treated, the malignant condition has not advanced too much and is not too extensive, and if he is fortunate enough to have the chronic form, he may survive for several or even for many years. He will probably need treatment from time to time, but the affected lymph nodes will continue to respond well.

Fig. 8: Roentgenograms of thorax in case 4.

Fig. 8a: Roentgenogram made on September 24, 1930, showing marked enlargement of mediastinal nodes. The patient was a young man, twenty-six years of age, who had been ill only six months. The cervical nodes were greatly enlarged, and the face and neck were engorged and cyanotic from venous obstruction. The retro-abdominal, axillary and inguinal also were extensively involved. The patient was pale and weak but his weight had not diminished.—Fig. 8b: Roentgenogram made on October 1, 1930, after roentgen treatment each day for six days. It shows extremely rapid and marked regression of the affected mediastinal nodes. This indicates great instability of the lymphoid system; when the lymph nodes are involved as extensively as this and when they retrogress as rapidly as they did in this case, the patient seldom can be expected to live long. In this case the patient died eight months later.
When, as is sometimes done, treatment is given only once or twice a week, the patient does not improve as rapidly or as much as he should; and when the quantitative dose of rays given to each field, whether this is done at one time or by the fractional method, is excessive, the affected lymphoid structures rapidly become resistant to the rays, and thenceforth the treatment becomes less and less effective. When excessive doses are avoided, the affected structures continue to respond indefinitely. It is true that, as time goes on, especially in the chronic form of lymphoblastoma, some increase in resistance of the lymphoid cells develops, but this is slow. In most cases, gradual failure of lymphoblastomatous lesions to respond to irradiation is due to (1) an advanced stage or terminal phase of the pathologic process and (2) excessive quantitative doses of rays within a given time.

**PROGNOSIS**

Survival depends chiefly on the three following factors: (1) the relative acuteness or chronicity of the malignant lymphoid process; (2) the extent of involvement and the stage which the condition has reached when it is recognized and when treatment is started and (3) the thoroughness and care with which the treatment is planned and given. Of these three factors the first two are much more important than the third, and the first is more important than the second. It must not be inferred that treatment is of small consequence; it is true that, in the average case, its influence on survival is not as great as might be desired (Fig. 8), but there is no doubt that, when patients receive sound treatment, their condition is much better and their symptoms can be kept under partial or complete control for long periods.

In cases of relatively acute lymphoblastoma the pathologic process runs a comparatively short course, and the time which elapses between the apparent onset of the disease and the death of the patient may vary between six months and three years; fortunately, the number of cases in this group is small. By far the largest group consists of patients who are afflicted with these conditions in a relatively subacute form, in which the course of the process extends from three to six years (Fig. 9). In a considerable number of cases the patients have the chronic form, in which the malignant condition may continue from six to ten, fifteen or twenty years, or even longer.

**SUMMARY**

Each variety of normal cell has a specific range of sensitiveness to roentgen rays. The different varieties of normal cells are listed in the order of their sensitiveness. The action of roentgen rays on
Fig. 9: Roentgenograms of the chest in case 5.

Fig. 9a: Roentgenogram made on July 29, 1921. It shows moderate enlargement of mediastinal nodes, principally on the right side. Besides this, some nodes in the neck, armpits and groins also were affected.—Fig. 9b: Roentgenogram made on September 28, 1921, after a course of roentgen treatment. It shows marked regression of the mediastinal nodes, and the cervical, axillary and inguinal nodes also had been correspondingly influenced by the treatment. Then the patient remained well and free from symptoms and lymphadenopathy until 1927.—Fig. 9c: Roentgenogram made on June 6, 1927. It shows fresh and considerable enlargement of mediastinal nodes. Roentgen treatment again caused these nodes to retrogress markedly. Then the patient was well until 1932 when weakness, pallor and gastro-intestinal symptoms developed and physical signs indicated probable involvement of retroperitoneal nodes. The cervical, axillary and inguinal nodes also had again enlarged. Roentgen treatment directed toward the upper two thirds of the abdomen and toward the chest was followed by substantial improvement.
cells is briefly described, lymphocytes being used as an example. Then the sensitiveness of different kinds of tumors is mentioned, and stress is laid on the close correspondence in sensitiveness between tumors and the normal cells from which different kinds of tumors are derived. Knowledge of the relative sensitiveness of different tumors often permits one to distinguish some tumors from others, and this is as true of thoracic and intrathoracic tumors as it is of tumors in general.

The more common clinical and roentgenologic features of Hodgkin's disease or lymphosarcoma of the chest are reviewed. Then the treatment of these conditions is discussed with reference to the anatomic arrangement of the fields, the quality and quantity of the rays. Finally, the principal factors which govern prognosis are mentioned.

RESUMEN

Cada variedad de célula normal tiene una esfera específica de sensibilidad a los rayos de Roentgen. Se cataloga las diferentes variedades de células normales en el orden de su sensibilidad. Se describe brevemente la acción de los rayos de Roentgen sobre las células, usando los linfocitos como ejemplo. Se menciona después la sensibilidad de diferentes clases de tumores, y se hace hincapié sobre la íntima correspondencia en sensibilidad que existe entre los tumores y las células normales de las que se derivan diferentes clases de tumores. El conocimiento de la relativa sensibilidad de diferentes tumores frecuentemente nos permite distinguir unos tumores de otros, y esto es tan cierto en tumores torácicos e intratorácicos como lo es en tumores en general.

Se repasa los rasgos clínicos y roentgenológicos más comunes de la enfermedad de Hodgkin o linfosarcoma del pecho. Se discute después el tratamiento de estos estados con respecto de la disposición anatómica de los campos y la calidad y cantidad de los rayos. Finalmente, se menciona los principales factores que determinan el pronóstico.

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which continued until 1936 when fever and loss of weight developed. More treatment again caused marked improvement. In 1937 the return of fever, itching and edema required additional treatment, and this again yielded considerable improvement. Finally, in 1938, the lymphoblastomatous process again became active in the abdomen and elsewhere, but roentgen treatment yielded only slight and transient improvement and the patient died late in the same year.
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