THE PRESENT STATUS OF ROENTGEN THERAPY *

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The present status of roentgen therapy depends upon many contributions to radiology by scientists in other fields. It would be impossible even to enumerate them. However, it is necessary to discuss past experiences in order to explain the rationale of modern methods of treatment.

In 1904 Bergonie and Tribondeau formulated a law which may be called the biological foundation for radium and roentgen ray treatment. They postulated, "Immature cells and cells in an active state of division are more sensitive to irradiation than are those that have acquired adult morphological and physiological characteristics." This law implies that the effect of the rays is to alter cellular functions by injury and that cells vary in their response according to their degree of differentiation in relationship to the quantity of irradiation which they absorb.

Most tissues of the body are continuously functioning and old cells are being replaced by new ones. In some tissues this takes place more rapidly than in others; therefore, normal tissues differ in the degree of their reaction to irradiation, destructibility or radiosensitivity. The same is true of pathological tissues, the cells of which, as a rule, are dividing more rapidly than those that are normal. Consequently, pathological tissues also vary in their degree of reaction to irradiation and usually are more radiosensitive than normal tissues. It is on the basis of this knowledge that in the past few years physicians have become interested in studying the histology of pathological tissues, especially tumors, to grade or classify them according to their degree of differentiation as indicative of their probable rate of growth, radiosensitivity, and curability.

The principal indications for roentgen therapy according to its biological effects are (1) to modify temporarily or to inhibit cellular functions so that physiological activities of tissues are altered, especially the secretory functions of glandular organs, and (2) to destroy pathological cells. In all probability, effects of irradiation which have been interpreted as stimulation are actually due to depression or inhibition of some functional activities of organs by cellular injury which results in or causes relative increase of other functions. It is obvious that the quantity or dose required to bring about these effects differs. Therefore, radiologists and physicists have sought ways for measuring radiation in order to apply it according to the reaction indicated, to interpret the effects upon tissue and clinical responses to treatment on the basis of known quantities administered under different and reproducible technical conditions.

In the early days of roentgen therapy, dosage was estimated by "trial

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and error" methods based upon the length of time of exposure according to voltage measured with spark-gaps and current by milliameters. The errors soon convinced radiologists that more accurate methods of determining quantity and quality of radiation were necessary in order to reproduce biological effects, especially after filters were introduced. Fluoroscopic, chemical, and photographic methods were used for some years. Soon it was apparent that the ideal method would be to measure radiation according to the actual energy of the rays, but this method has not been practical because of the difficulty of measuring such small amounts of energy. However, it has been found that the power of the rays to ionize air may be utilized to measure radiation accurately and easily. During the past fifteen years instruments have been developed for measuring ionization in air, under specified conditions, in an internationally accepted unit of quantity, the "roentgen." This unit is established by means of large open-air ionization chambers constructed according to prescribed specifications. Standard measuring apparatus of this type is available in several physical laboratories in this country, including the central one at the National Bureau of Standards in Washington, D. C.

However, large ionization chambers cannot be used by radiologists in practice. Therefore, secondary standards or "dosemeters" have been developed. These instruments are equipped with thimble-sized ionization chambers also built according to definite specifications, the most important of which being that the walls of the chamber must have a coefficient of absorption for roentgen rays approaching that of air. Dosemeters are calibrated by comparison with large standard chambers; therefore, they may be used to measure quantities of radiation independent of qualities used in roentgen therapy. In practice, radiologists may use dosemeters to determine and calibrate the roentgen output in air of their apparatus or measure the dose administered by placing the ionization chamber of the instrument directly upon the skin of patients in the field of radiation.

Dosemeters of this type also are used to measure and chart the relative difference between the quantity of radiation on the surface and that which penetrates to different depths or is absorbed. In this country, surface dose and depth absorption charts have been standardized for most of the technical conditions used in treatment; thus, radiologists now can estimate the amount of radiation administered on or in any part of the body.

However, the quantity of radiation which penetrates to different depths depends upon the quality of the rays according to voltage and filtration. Suggestions have been made for expressing quality in terms of wave-lengths determined by spectrography. But since beams of roentgen rays are not homogeneous, such terms as angstroms or minimum, average and effective wave-length have not been acceptable to physicists. Nevertheless, radiologists require some method for defining quality and ways for determining it in practice. It is agreed that quality should be designated by "half value layer" in metals. This value is expressed as the thickness in millimeters of aluminum, copper, or lead that will absorb one-half of the quantity of a beam of roentgen rays.

It now is possible for radiologists and physicists to understand each other and to express quantity and quality of radiation in defined units, to measure and calibrate apparatus for any technical conditions according to these standards, to estimate the amount of radiation administered to any part of the body, to judge biological reactions in tissues on the basis of known quantities of radiation absorbed into them and to reproduce the physical conditions known to create certain biological effects.

In planning treatment according to the indications previously mentioned, radiologists may select the quality and the quantity of radiation that experience has proved will bring about desired effects according to the location and relative radiosensitivity of the tissues to be treated. In many instances the disease is located deep in the body, and it would be impossible to give the necessary quantity to it through a single portal of entry without damage to overlying structures. To overcome this difficulty the rays are focused at different angles upon the diseased area through several portals by what has been called "cross-fire technic," thus increasing the quantity in the region by the multiple of the number of portals used.

Although in planning roentgen therapy it is necessary to take into consideration the physical and technical factors influencing quality and quantity, it is equally important to take into account the rate of administration in relation to the rate of cellular division and multiplication in pathological tissues, especially cancers. When roentgen therapy passed the empirical stage of trial and was based upon knowledge of physical aspects, it was thought necessary in the treatment of cancer to administer in the shortest possible time as large quantities of irradiation as normal tissues could tolerate. This so-called "massive dose" technic has been supplanted in recent years by prolonged or fractionated methods with improvement in results.

The newer methods were developed when it was realized that normal tissues recover from the injurious effects of irradiation more rapidly than those that are pathologic, because abnormal cells are dividing more rapidly and are most radiosensitive in embryonic phases. In other words, more pathological cells in radiosensitive stages are affected when treatment is prolonged and there is less permanent damage to normal structures. Therefore, in administering roentgen therapy for conditions for which large dosages are indicated, the skin tolerance is used as a basis for determining the limitations of treatment. It has been customary to use as a biological standard of dosage the quantity of radiation that, when given at one time, will result in redness or erythema of the skin in about two weeks. This reaction also varies according to quality, because the quantity of radiation absorbed and back-scattered in superficial layers is not independent of wave lengths of roentgen rays. For example, when low voltage and light filtration are used, an erythema reaction may be produced with 400 roentgens given at one time, but with higher voltage and heavier filters, 800 roentgens will be required to produce a similar reaction. However, the recovery rate of the skin from irradiation injury permits smaller doses to be given over a long period of time without serious consequences, so that the total quantity can be increased considerably in comparison with the amount that would result in skin damage if given at one time. When prolonged treatment is given in order to administer large quantities of roentgen rays, high voltage and thick filters usually are used. The daily dose customarily given to one or more skin areas may be about 250 roentgens or less. By this procedure, it is possible to administer several erythema skin doses to each area and, under certain technical conditions, from 2,000 to 4,000 or even more roentgens. Thus, the total quantity that can be delivered to tissues by this procedure is increased considerably.

Consideration of the biological effects of radiation is essential also for the regulation of dosage of roentgen rays indicated for the treatment of different types of disease. Experience has proved that modification of the secretory activities of certain glandular organs such as the pituitary gland or ovary may be influenced by very small doses of irradiation. Inflammations in many locations and diseases of the blood cell forming organs usually are treated by small or moderate dosage. Although malignant tumors vary somewhat in their radiosensitivity, they require large quantities of irradiation to destroy them, sometimes greater than can be administered without damage to normal tissues; therefore, it may be necessary to augment roentgen therapy with radium.

Many types of roentgen ray apparatus now are available, having been designed primarily to produce different qualities of radiation in sufficient quantities.

The least penetrating rays used in treatment are "Grenz" or "Borderline" rays produced at 10 kilovolts from a water cooled tube having a lithium or soda glass window. The radiation is absorbed very superficially, causes little reaction in subcutaneous tissues, and therefore, the usefulness of this type of apparatus seems to be limited to the treatment of some skin diseases.

Another type of low voltage apparatus, operating at 50 kilovolts, has been used during the past few years for contact treatment. The apparatus was designed primarily to administer large doses of roentgen rays quickly to small superficial lesions, especially cancers, and to replace radium treatment which takes considerably longer to produce similar clinical effects. The shock-proof water or air cooled tubes are so constructed that their anode-focus to surface distance is very short, being only 18 millimeters; therefore, the radiation output is as high as 8,000 roentgens per minute without added filters and in direct contact. Filters of 1.0 or 2.5 millimeters of aluminum may be added to change the quality. Radiations of these qualities used in contact roentgen therapy also are absorbed superficially; therefore, there is little damage to tissues underlying lesions even when treated with large quantities. The tube may be introduced into body cavities or surgical openings to irradiate in locations otherwise inaccessible.

What now is called "intermediate therapy" is given at from 80 to 140 kilovolts. This type of equipment has been in use since the beginning of roentgen therapy. The quality at 80 to 100 kilovolts without filter or with a few millimeters of aluminum added is useful for the treatment of many superficial diseases and is preferred by dermatologists. When 120 to 140 kilovolts are used, the filtration is increased from 4.0 millimeters of aluminum to 0.25 millimeters of copper. Roentgen rays of this quality are generally used for the treatment of inflammations and blood diseases, but no longer are considered to be effective for treatment of malignant tumors situated deep in the body because about 90 per cent of the radiation is absorbed in the first 10 centimeters of tissue.

The demand for radiation of greater penetrability led to the development in about 1920 of "deep therapy" apparatus operating at 200 kilovolts. This type of equipment is now in general use, especially for the treatment of deeply situated diseases. Usually filters of from 0.5 to 2.0 millimeters of copper are used. The 10 centimeter depth dose with this quality is from 25 to 35 per cent of the surface dose, depending upon the filter, focus-skin distance, and the size and shape of the field of application. Thus, the total depth dose that can be administered by cross-fire methods with this quality may be equal to or greater than the surface dose.

It probably was physicists' inquisitiveness about the properties of roentgen rays approaching the quality of Gamma rays of radium and the challenge to engineers to meet their demands that has led to the development in the past few years of apparatus to operate at from 400 to 1,000 or more kilovolts. Apparatus in the 1,000 kilovolt range has been found to have certain advantages: (1) There is less back-scattered radiation to the surface because of the forward direction of the scattered radiation and therefore better skin tolerance. (2) The greater penetrability of the rays increases the depth dose relative to surface dose to 40 or 50 per cent at 10 centimeters for 10x10 cm. portals. (3) The depth dose is relatively independent of the size of portals of entry ordinarily used in treatment, because back and lateral scattering is not great in proportion to the forward projection of the radiation. This permits many small fields to be selected to cross-fire deeply situated regions with less damage to overlying structures. (4) The radiation is heavily filtered and therefore more homogeneous than qualities produced at lower voltages, and it is more evenly distributed in tissues. Apparatus operating at voltages from 700 to 1,000 kilovolts is being used for roentgen therapy in about a dozen institutions in this country. Although not enough time has elapsed to pass final judgment about their effectiveness, reports indicate improvement over lower voltage equipment, especially for the treatment of deep-seated malignant tumors.

Neutron radiation, produced at several million volts by cyclotrons, also has been used to treat patients suffering from cancer. The impression seems to be that the reactions of normal and pathological tissues to neutron and supervoltage roentgen radiation are quite similar.

It may be mentioned at this point that during the past few years since the development of shock-proof apparatus, there has been renewed interest in the administration of roentgen therapy intra-orally and intravaginally by using suitable especially designed cones. The results indicate that in many cases this technic may be preferable to the use of radium for diseases in these locations.

The different types of apparatus now available for roentgen therapy furnish radiologists with a wide range of quality and sufficient quantity. Each has its indications and usefulness. The limitations of roentgen therapy are not attributable to physical factors, but are biological. There is no conclusive evidence that different qualities of roentgen rays have different or selective biological effects. Variations in reactions of tissues irradiated by different qualities are explainable on the basis of quantity or energy absorbed. Therefore, the voltage, filtration, and other technical factors used in roentgen therapy must be chosen according to the quantity that will be effective at the location of the lesion, and the treatment given at rates commensurate with the character of the disease and the reactions in the normal tissues which surround it.

One limitation is attributable to the fact that many pathological tissues such as low grade, slowly growing malignant tumors are little, if any, more radiosensitive than normal tissues in which they originate and grow. Under such circumstances, it may be impossible to irradiate adequately diseased areas without equal damage to normal or vital structures.

The principal limitation to treatment usually is the anatomical extent of the disease. When pathological tissues are accessible and localized so that vital organs are not extensively involved they may be eradicated by irradiation. But unfortunately it is characteristic of cancers and allied diseases not to remain localized for very long, but to invade progressively normal structures in their neighborhood. In addition, viable cells from them may be transported in the lymph or blood streams to distant tissues where new growths or metastases develop with the same potentialities to destroy life as the parent tumor. Although primary malignant tumors may be destroyed, any secondary or metastatic growths outside of the irradiated area or in inaccessible locations could not be affected.

One of the most important problems confronting the medical profession is the treatment of cancer and allied diseases. Operations, radium, or roentgen therapy in their present status are not the final answer because of the limitations discussed. The magnitude of the problem may be

CURABILITY OF CANCER

Organ	*Relative Incidence*	*Deaths in U. S. 1931*	*Present Rate of Selected Cases (per cent)*	*5 Year Cures Average (per cent)*	*Possible Cures Under Ideal Conditions (per cent)*
Stomach	22	25,397	5	1	5
Intestine	9.4	10,953	5	2	10
Rectum	4.3	5,451	15	2	15
Uterus	12	14,464	35	10	40
Breast	9.2	11,444	33	10	35
Liver, gall bladder	8.8	10,290	2	1	5
Prostate	3.9	4,924	5	1	10
Bladder	3.1	3,874	35	15	40
Intraoral	3	3,563	25	15	50
Tongue	0.8	919	25	10	50
Lip	0.5	630	80	50	95
Pharynx	.9	1,004	5	1	25
Skin	2.5	2,986	70	60	85
Pancreas	2.5	3,139	1	?	2
Lung	2.2	2,846	.1	?	1
Esophagus	1.8	2,038	.1	?	1
Ovary	1.5	2,051	5	1	10
Kidney-adrenal	1.4	1,651	2	1	5
Bone sarcoma	1.4	1,644	5	2	10
Thyroid	1	?	2	1	5
Larynx	.8	925	20	5	50
Brain	.7	844	5	2	10
Testis	.2	345	29	5	40
Lymphosarcoma	3?	?	5	1	10

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illustrated by a table compiled by James Ewing. He describes it as follows: "I have prepared the subjoined table of approximate estimates of the relative frequency of the different forms of cancer, their present rate of cure in the best clinics, the average rate of cure, and the possible rate of cure under ideal conditions. These ideal conditions include a highly educated, intelligent public, skillful and experienced specialists, and the best of modern equipment. The figures showing incidence and deaths are from the U. S. census report for 1931."

This table indicates how extensive malignant diseases usually have become by the time they are discovered or treated. Of course, no deductions can be made from it in regard to the relative roles of radiation therapy or other methods in bringing about cures. Unquestionably many patients with cancer have been cured by irradiation, but it is obvious that a vast majority must be incurable by any known procedures. Nevertheless, among the principal indications and greatest benefits of roentgen therapy is the palliation and prolongation of life and economic usefulness of people suffering from diseases that cannot be treated so succesfully in any other way. Apparently it is too fantastic to hope that something will be found which, though non-toxic for normal tissues, will have selective absorption and toxicity for cancer cells or render them more radiosensitive yet. Recent investigations in the production of artificially radioactive salts and their clinical trial suggest the possibility.

Although roentgen therapy is beneficial for malignant diseases, its scope is broadening in other fields as we learn more about physiology, the etiology, and pathology of diseases, the biological effects of the rays upon tissues under controlled physical conditions, and as technics are improved. In its present status roentgen therapy is being given for many diseases, a few of which may be mentioned briefly to illustrate its applicability and effectiveness.

There is a list of almost three hundred different diseases of the skin which are amenable to roentgen therapy.

Inflammations caused by many kinds of infectious agents affecting different tissues may be benefited, pain relieved, fever reduced, and the course of the disease shortened. Such conditions as erysipelas, furuncles, carbuncles, sinusitis, mastoiditis, and inflammations of lymph glands respond very well. Gas gangrene is a serious complication of industrial and war wounds and has been the cause of many deaths but roentgen therapy, when given early, has definitely reduced the mortality rate. Although vaccines and new chemical compounds are used successfully in the treatment of some types of pneumonia, roentgen therapy also has been beneficial. Conditions such as encephalitis and inflammations of the salivary glands sometimes are due to viruses and are successfully treated in early stages. It never has been satisfactorily demonstrated that roentgen rays are directly germicidal in the dosages used in treatment of inflammations. It is theorized, although cooperative experimental evidence is lacking, that when infected tissues are irradiated the infiltrating phagocytes in them are destroyed so that intracellular anti-bodies are liberated to combat promptly the infectious agents.

Progress which has been made in endocrinology during the past two decades has demonstrated that roentgen therapy may modify the functional activities of glands of internal secretion, abnormalities of which are responsible for constitutional disturbances. Dysfunctions of the pituitary gland, gonads, and adrenal glands cause certain menstrual and growth disturbances which may be corrected or their progress aborted by irradiation. In this connection the treatment of uterine fibromyomas may be mentioned, which is successful in ninety per cent of properly selected cases. The symptoms of exophthalmic goiter or hyperthyroidism attributed to dysfunction of the thyroid gland may be relieved by roentgen therapy. The treatment is indicated especially when operations may be unduly hazardous or have been unsuccessful.

There are diseases of the bone marrow, spleen, and lymph glands in which blood corpuscles originate, such as myelogenous and lymphogenous leukemias, polycythemia and Hodgkins' granuloma, the causes of which are unknown. They are considered to be allied with cancer and ultimately are fatal. Roentgen therapy is the most successful treatment for relief of distressing symptoms and for prolongation of life.

The present status of roentgen therapy may be attributed to the development of many types of apparatus by ingenious engineers, to studies of the properties of radiation by meticulous physicists, to investigations of the effects upon cellular functions by inquisitive biologists and pathologists, and to the correlation and clinical application of accumulated knowledge by radiologists.

The causes of many diseases and functional disturbances are unknown; therefore, they are treated empirically and symptomatically. When the etiology of a disease is revealed, usually ways of prevention and successful treatment are developed. Future progress in medicine depends upon continued investigation and collaboration of biologists, chemists, and physicists who are familiar with clinical problems.