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The Biologic effects of roentgen rays and radium upon normal tissues

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THE BIOLOGICAL EFFECTS OF ROENTGEN RAYS

and

RADIUM

UPON NORMAL TISSUES

by

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2. INTRODUCTION

The development of the induction coil with mechanical interrupter in 1853 by Faraday, the static machine in 1860 by Wimhurst, and the mercury air pump in 1865 by Geisler and Sprengel were the essential factors in developing the Hittorf tube in 1869 and the Crookes tube in 1878. Crookes described cathode rays as being emitted from the negative pole and absorbed within the tube by thin layers of material. It was these developments and findings that lead to the discovery of x-rays.

It was on the eighth of November, 1895, that Wilhelm Konrad Roentgen, a professore of physics at the University of Wurzburg, Germany discovered that a partially evacuated glass vessel through which a current at about 10,000 volts was being passed, emitted a radiation which could penetrate cardboard, wood, and paper and blacken a photographic paper. The nature of the radiation was not known and term "X-radiation" was applied to it by Roentgen. He described these rays as possessing the following properties:

1. Fluorescence of barium platinocyanide and certain other crystals.
2. Blackening of photographic emulsion.
3. Ionization of air.
4. Absorption of rays according to the square of the density of the materials traversed.

It was in February 1896 that Becquerel working in Paris noted the spontaneous emission of radiation from uranium ores and in 1898 his students, Marie and Pierre Curie, isolated the radioactive material from these ores and called it radium.

A short time after the discoveries of Roentgen and The Curies' it was noted that roentgen rays and radium had biological effects. Roentgen rays were at first demonstrated to the public at fairs and even in one of the leading department stores in New York City in this country by the demonstrator placing his hands between the tube and a fluorescent screen. The first ill effects noted by these early pioneers were those of reddening of the skin associated with vesiculation, and epilation with pigmentation. Roentgen in his experiments protected himself with lead and zinc plates between himself and the tube. Many others of the pioneers were equally careful in protecting themselves as was Dr. Francis Williams of Boston from 1896 until the present time. Dr. Walter James Dodd, a colleague of Dr. Williams, did not protect himself and was badly burned and died from the effects in 1916. Many other pioneer radiologists suffered from roentgen ray-burns and died from the

effects which usually lead to roentgen cancer and radiation anemia. Madame Curie died in July of 1934 suffering from aplastic anemia. Over-radiation often resulted in severe local damage to the patient and in April 1896 Daniels noted twenty-one days after taking the skull of Dr. W. L. Dudley, epilation of the scalp occurred. Edison in 1896 reported a man working with the fluorscope who developed sore eyes and intractable lesions of the hands and skin about the face. He also noted flashes of light in his eyes after working with the rays due to the fluorescence of the retina, and after noting these effects, he decided not to work with these rays until more was known of their effects. (42)

Becquerel in 1900 developed a temporary ulceration of the skin about one week after carrying a tube of radium bromide in his vest pocket. Dermatologists and a few others soon noted that roentgen rays and radium were powerful therapeutic agents capable of improving a wide variety of lesions and doing irreparable damage to normal tissues. In an editorial in the Journal of the American Medical Association on February 15th, 1896, the opinion was expressed that the new rays may possibly have a therapeutic effect. The first use of radium in this country was by Dr. Francis Williams of Boston at the suggestion of Dr. William Rollins about

1900. It was used on a rodent ulcer but as the salts then obtained were not powerful enough to be efficent, it had no effect on the ulcer and only caused slight reddening of the skin. Later Dr. Williams reported forty-two cases treated by pure radium bromide in the Medical News, February 6th, 1904. (17) Other early workers to note the effects of radiation on tissues and to study them experimentally were Chaluppecky who in 1897 demonstrated that irradiated rabbits developed anterior polar lenticular opacities fifty days after exposure (18); Perthes in 1903 noted that the growth of chicken's wing exposed to rotentgen irradiation when the chicken was one day old was greatly reduced (10); Danyz in 1903 was the first worker to study the effects of radium upon the tissues of the central nervous system (93); and Heinke in 1904 made the first careful histological studies on the blood.

These early beginnings were to mark the opening of new fields of research and applications of new methods to diagnosis and therapy that were undreamed of by most observers as to what their extent would be in the forty years following their discovery.

Much has been written about the biological effects of the various types of radiation and the

researches covering this field. It is the will of the author to review the literature to a limited extent and to present some of the observations made concerning the effects of roentgen rays and radium on normal tissues considering the physico-chemical, microscopic and gross changes as related by various observers.

3. PHYSICO-CHEMICAL EFFECTS OF ROENTGEN RAYS AND RADIUM

The most logical method of approach in discussing the physico-chemical effects of radiation is to deal with the effects upon the individual cells and the changes brought about in these cells.

In discussing these effects it is desirable to give a brief account of the structure of a typical animal cell. A cell may be defined as an organized protoplasmic unit; containing differentiated nucleus with a nuclear membrane and nucleolus; cytoplasm, cytoplasmic inclusions containing granules made up of microsomes and macrosomes, mitochondria, golgi apparatus and chromidia; and an external limiting membrane. The cell membrane acts as protection for the cell body and is a semi-permeable membrane which is probably formed by a surface condensation of certain elements of the cytoplasm. Permeability of the cell membrane to ions or colloidal micellae is observed to differ when the cell is in the "active" or "resting state". The chemical nature of cell membrane is unknown but experimental evidence points to the fact that it is a system of at least two essential phases, one a watery solution of protein, the other a lipid phase. In either the active or the resting state of the cell, the membrane

is permeable to substances soluble in water and also in oils or lipoids, such as urea, oxygen, carbon dioxide, some ammonia salts, alcohol and chloroform. In the active state, it is permeable to salt, glucose, and amino acids and in the resting state it is impermeable to most salts (except certain salts of ammonium) glucose and amino acids. The cytoplasm is especially concerned with nourishment of the cell and the mitochondria enter definitely into reproduction as in fertilization these and the nucleus of the sperm alone enter the ovum. The chief duty of the nucleus is to carry on the characteristics of the cell and its chief concern is in cell division carrying the chromosomes from it to the next generation (20).

The law of conservation of energy tells us that if a change has been brought about in a system by external means, then some energy must have been supplied to the system from the exterior. Thus, if a living cell is altered in any way by exposure to radiation, it must have received some energy which at least initiated the change. The living cell exposed to radiation receives a small amount of energy which initiates certain changes requiring much more energy to bring to completion the changes already begun, this energy being supplied by chemical changes in the cells (33).

The ordinary chemical reactions of x-rays and the beta and gamma rays from radio active substances are considered to be due to the same initial cause -- ionization (20). Ionization is the only thing we know of to which we may attribute all of the effects of radiation. Whatever the mechanism of the biological action of radiation may be, we know definitely that ions are produced in the material and that the presence of these ions is apt to produce chemical changes or electrical disturbances which must affect the biological processes (33).

The biological action of radiation may be accounted for by the chemical effects which radiation produces. The sequence of events may be assumed to be first ionization of the tissues, followed by chemical changes and this followed in turn by biological changes with further chemical changes resulting from these biological changes and so forming a vicious circle so as to speak. This point of view accounts at least to some extent, for the delay of effects of radiation as seen upon living organisms (33).

Since cell protoplasm is very largely a carefully adjusted system of colloids and proteins are emulsoid colloids, it is well to consider the outstanding results of the chemical actions of radiations upon them which

have a direct bearing upon the biological effects.

Some of the earliest experiments of the action of radiation on colloids were carried out in 1903 by Hardy. Using two samples of serum globulins, one of which had been rendered alkaline by the use of ammonia and the other acid by use of dilute acetic acid and exposed to alpha radiation, he found that the globulin that is alkaline or negatively charged is set to a gel in three minutes apparently by action of the positive charged alpha particles. The acid mixture became clearer and is explained by the fact that the positive charges carried by the elements of the dispersed phase have their action reinforced (20). The effect of beta and gamma rays is to decrease the solubility of proteins regardless of the charge (33).

Colwell and Russ in 1912 investigated the action of x-rays upon the organic colloids such as egg white, serum, albumin and starch and in all of these noted a marked diminution in viscosity.

It has been found that protein solutions were more acid after exposure to radium but this may be qualified by the statement that unbuffered solutions exposed to x-rays are made more acid on the alkaline side and more alkaline on the acid side of the isoelectric point.(33)

The viscosity of serum albumin is increased only at the isoelectric point after exposure to x-rays while globulin shows an increase on both sides (33).

It is generally concluded that x-rays and radium do produce damage to the cell membrane so that in fixed sections the cell outline is lost and it has been shown as early as 1916 that the permeability is altered by exposure to x-rays and radium. In the case of the red blood cell, it is known to be normally impermeable to hemoglobin and to cations and permeable to such anions as chloride and bicarbonate.

In 1916 Harriman showed that blood agar was hemolysed on exposure to beta-radiation from radium after long periods of time. It has also been shown by others that hemolysis takes place (20).

In examining the chloride content of the red blood corpuscles in the human after irradiation of twenty cases, there was found evidence of water-inflow, and in the majority of cases, there was also a chloride migration into the cells. These observed facts clearly point to a disturbance of the physical functions of the limiting membrane(20).

The most striking biological effects of radiation are upon the chromatin and the nucleus. The chromatin forms the main constituent of chromosomes which are

determiners of the hereditary characters. In using the *Drosophila*, it was found that x-ray treatment affects the distribution of the chromosomes during maturation of the egg which may develop into an adult that produces offspring -- the irregular distribution of the chromosomes being inherited. This shows how x-rays may produce a permanent change in a cell without altering its vitality.

It was shown that the spermatozoa were most susceptible at the time that the chromosomes (bodies from chromatin as a result of cell division and reproduction) became arranged in pairs prior to the first maturation or during the growth period (74).

It has been shown that the resting nucleus is more resistant to the effects of radiation than the nucleus during the early stage of mitosis. It is especially sensitive during the metaphase (65).

Mottram in 1913 showed that when cells were exposed to radiation during mitosis, they were more affected than when exposed during the non-dividing state. This was again demonstrated in 1933 (80). However, in sufficient doses, it will so injure the nucleus of the cell so as to prevent further mitosis (100).

The work of Nadson on living yeast cells gives a clear picture of the progressive changes in the cell which

begin almost as soon as the exposure begins and terminates in the death of the cell. First there is seen an increase in the number of fat droplets of the cell which is not injurious if the radiation is not prolonged. Next, the protoplasm becomes turbid due to the appearance of granules undoubtedly protein in nature. What has happened is that the colloidal protein has undergone a partial change in solubility, that is, it has become insoluble. These changes are at first reversible for the turbidity may disappear in which case the cell recovers. With longer exposures, the turbidity does not seem to increase further, but the number of protein particles does. The permeability of the cell membrane at first decreases; after long exposures it increases and is accompanied by a coagulation of protoplasm. In other kinds of cells, there may be seen an extensive vacuolation of the protoplasm and a breaking up of the filamentous mitochondria into granules, a reversible reaction (89).

The course of the death curve of the cells is the same whether x-rays or gamma rays of radium are used as the lethal agent and it is believed that wave length is not a determining factor in the rate of death because x-ray beams of equal intensity but of different wave lengths produce the same quantitative biological effect

on *Drosophila* eggs (90,91).

In conclusion as regards the mode of action of radiations upon living tissues, various views have been put forward from time to time. Probably no one theory can explain all of the phenomena but what does seem clearly established is that x-rays and the gamma radiations from radium have a marked effect upon certain classes of colloids among which are proteins and starch. Proteins undergo marked diminution in viscosity and are more easily precipitable after radiation than before. It seems not improbable that certainly one of the effects of radiation is a disturbance of the colloidal equilibrium in cells with consequent devitalization. If not carried too far, the cell may recover but if certain limits are exceeded, the damage is irreparable and the intra-cellular enzymes may then come into play, their action being of a destructive character upon devitalized cell protoplasm (118).

4. GROSS AND MICROSCOPIC EFFECTS OF
ROENTGEN RAYS AND RADIUM ON THE FOLLOWING
SYSTEMS

a. INTEGUMENTARY SYSTEM

Following the discovery of x-rays by Roentgen in 1895 and radium by the Curies in 1898 the first effects of these radiations were noted on the skin and in many instances these effects have proven to have been very saddening for many of those who came in contact with them.

Marcuse in 1896 probably made the first microscopic examination of the effects of roentgen irradiation on the skin. He examined a case of roentgen ray alopecia and dermatitis and in the hair he found signs of degeneration in those that were falling out. The root was fibrillated, the sheath swollen, the characteristic cupping of the base absent and in the shaft the outlines of structure were entirely gone, the line of the medulla being completely lost. Gilchrist in 1897 examined portions taken from the skin in x-ray dermatitis, these portions showing the pathologic picture of chronic inflammation. The horny layer was thickened and partly detached and contained a large number of brown pigment granules in the exfoliating epithelium. The vessels of the corium were dilated and a number of pigment cells in the upper layers were almost as great as in the skin of a negro (121).

Many descriptions of the effects of radiations upon

the skin have been written but these early writings serve as the most striking due to the fact that the reactions were contributed to so many other causes and the descriptions are most typical of the reaction of the skin to x-rays and radium. Many of these first reactions were seen in demonstrators who were showing the rays to the public at fairs and exhibitions. One of these accounts which is typical of many reports of early mishaps appeared in Nature October 29, 1896 and is summarized as follows:

The writer was employed as an x-ray demonstrator at the Indian exhibition in London in 1896. He began his work in May 1896 and was exposed daily for several hours. He suffered no apparent injury for two or three weeks but at the end of this time there appeared little blisters of dark color under the skin of the right hand which gradually became very irritating and the skin red and inflamed. The only measure which would relieve the severe pain was to put the hand into very cold water. Soon the pain became almost unbearable and the patient was almost to the point of giving up his work when he was recommended to use some type of proprietary ointment which gave him relief during the remainder of his engagement.

The skin of the fingers became yellow and parchment-like and finally peeled. In the middle of July the finger tips with the skin showing signs of marked discomfort at this time only partially relieved by the discharge of a copious, colorless foul smelling exudate came from beneath the nails which continued were shed a few weeks later. In the middle of August the left hand began to show signs of trouble similar to the right and the skin of the right having been shed for a third time the patient decided to try the effect of lanoline. This was rubbed in well and protected with kid gloves. From then until this was written, October 17, the patient was much more comfortable.

Many matyrs of x-ray suffered just such lesions as has been described only to develop intractable skin cancer ten to twenty years later and die of this condition.

Of the many causes suggested other than x-rays themselves are listed as follows:

1. Ultra-violet light given off from the Crookes tube.
2. Platinum particles from the tube.
3. Cathode rays.
4. Electric induction from the high tension currents.
5. Formation of ozone in the tissues.
6. Decomposition of water in the tissues.
7. Heat.
8. Idiosyncrasy: Even in 1897 it was said that some persons appear wholly insensitive.
9. Platinocyanides used in the fluorescent screens.
10. Faulty technique.
11. Trophic nerve changes.
12. De-electrification of tissues.

It was also suggested by Frei of Boston that x-rays generated by a static machine instead of an induction coil were without ill effects. In a communication which he made to the Electrical Engineer the title of his subject was,

"X-rays harmless with the Static Machine".

Many patients suffered from severe x-ray burns in the early days resulting from over-exposure during the taking of a part. From this many lawsuits resulted even in the first years of its use. Gradually the causative factors were corrected and for the past 30 years it seems almost inexcusable for a burn to develop from an exposure in doing the ordinary routine work with modern x-ray equipment but even today on rare occasions patients will allege x-ray burns if used by an inexperienced operator or if some fault has arisen in technique (21).

The histological changes following repeated x-ray exposures have been investigated by (127) who investigated the sequence of changes occurring in chronic x-ray dermatitis and controlled his histological findings in the human by experimental work on guinea pigs and rats. Experimentally the earliest demonstrable change histologically is a marked swelling of the collagen of the corium and subcutaneous tissue. The bundles of collagen fibers swell and there is coalescence of the individual fibers with a compact, refractory greatly thickened corium resulting. In guinea pigs this effect is visible after a single exposure in from 48 to 72 hours and reaches a maximum in 6 to 8 days. This change is accompanied by a marked shrinkage of the skin. This effect on collagen seems to be specific and can be

observed in the collagenous walls of blood vessels and the stroma of cutaneous appendages. (127)

Wolbach considers the swelling of the collagen to be due to a change in the osmotic relations. In support of this view the epidermis shows no change and Wolbach considers the epidermal lesions to be secondary to changes in the lymphatics and capillaries caused by swelling of the collagen. This altered connective tissue does not regenerate but new connective tissue is laid down by the surviving and ingrowing fibroblasts leading to the shrunken indurated condition seen in x-ray dermatitis.

Changes in the epidermis are visible on and after the fourth day and consist of swelling of the glands accompanied by mitotic division of the cells. In the superficial layers of the corium where the maximum effect of the radiation takes place minute necrotic foci are formed which produce a local polymorphonuclear infiltration. Microscopically these necrotic areas can be seen filled with a proliferated epidermis 12 days after a single exposure. There is a more or less permanent increase in the thickness of the corium brought about by the multiplication of fibroblasts and formation of new collagen between the old bundles of collagen. It is probable that a repetition of the effects just described occur in the formation of a chronic x-ray dermatitis.

A chronic x-ray dermatitis as seen in old workers in the field will show histologically complete loss of the appendages of the epidermis; replacement of the normal collagen by a dense hyaline collagen rich in elastic fibers and poor in cells; obliterative changes in the blood vessels of the corium and subcutaneous tissues; necrotic areas of various sizes in the corium immediately beneath the epidermis generally in the neighborhood of thrombosed telangiectases; and in response to the necrosis occurring in the corium reparative proliferation occurs in the epidermis with frequent regeneration of the epidermis beneath these thrombosed telangiectases or small masses of necrotic corium. These small necroses containing thrombosed telangiectases may become completely separated from the skin by a layer of the regenerated epidermis and persist for a time as dark spots until cast off.

Immediate change in one of these small necrotic areas is a focus of localized edema beneath the epidermis, therefore, the epidermis is separated from the corium by an edematous area containing only necrotic cells and often infiltrated with fibrous tissue. The probably shrinkage of the collagen producing a progressive obliteration of the capillaries leads to formation of these small necrotic areas. No attempt is made at repair

of these small areas by organization of connective tissue cells because of the changes present in the deeper tissues. Epidermis is soon regenerated over the gap so the effect of these necrosis is to produce a downgrowth of epidermis with the proliferated epidermis becoming so altered as to produce a thickening and imperfect keratinization so that the superficial cells remain attached to one another and give rise to masses of imperfectly keratinized fused epithelial cells suggestive of the origin of the hyperkeratoses, a conspicuous feature in chronic x-ray dermatitis (127).

Pohle (98) described four cycles of skin response to x-radiation the first appearing in 12 to 24 hours and then disappearing entirely, the second in 10 to 14 days, the third in 30 to 40 days and the fourth a few months to several years later. Both Pohle (98) and Clark (19) describe four degrees of skin reaction the first degree showing no signs of inflammation but showing epilation followed by tanning and lasting 2 to 4 weeks followed by recovery; the second showing moderate erythema with definite vascular dilatation and a sensation of increased temperature in the treated area with accompanying epilation and pigmentation lasting 6 to 12 weeks; the third showing a reddish blue erythema with vesiculation, epilation, loss of sebaceous and sweat

glands healing in 8 to 15 weeks with a thin epilated scar showing telangiectases with the danger of a late reaction occurring; and the fourth showing a reddish blue almost cyanotic erythema with vesiculation and necrosis developing into an ulcer that is most painful. The prognosis in this last type of case is doubtful as to recovery. Microscopically an acute ulcer can present the same changes as have been described as taking place in cumulative doses over a long period of time and this probably explains the tendency of both to end in malignant degeneration.

Another type of reaction seen may be termed the "late reaction" and the meaning given to it is the appearance of lesions of greater or lesser severity a considerable time after the cessation of radiation and corresponds to the fourth cycle described by Pohle. This reaction may develop from six months to several years after the cessation of radiation and range from telangiectases to a fatal ulceration. The telangiectases usually appear in from one to three years after radiation. It has been suggested that telangiectases are local attempts at compensatory vasodilatation owing to interference with the circulation in the deeper parts of the skin and subcutaneous tissue. These may continue to develop for several months to one or two years but

generally after this they tend to regress. Telangiectases may vary considerably in degree from a few more or less isolated vessels to extensive areas of deep red color that are covered with dilated blood vessels. Another common late lesion is atrophy of the skin with the skin showing the absence of sweat glands, sebaceous glands, and hair follicles with the skin acquiring a papery like appearance, often though not always, it is associated with telangiectases. The late ulcerations developing following a course of therapy are now commonly agreed to be due to a progressive endarteritis and lymphangitis set up by the radiations and associated with changes in the connective tissue in the deeper parts of the skin (21).

Many of these lesions appeared following using the old biologic unit of the erythema dose because the erythema produced is a vaso-dilatory response of the blood vessels and in many instances it was found that many individuals were more resistant to show this response and as a result of the damage to the deeper tissues were more apt to show the late reaction. However, this has been done away with the present method of measurement of x-rays.

The action of radium upon the skin has the same

effects as those that have just been discussed. Chronic changes taking place in the skin are most often seen in those who make radium molds or applicators or those who handle the radium in any way.

Ordway in 1915 recorded the experiences of a number of radium workers who were employed in handling radium applicators for therapeutic purposes. The symptoms were usually very insidious the first signs being noted were a blunting of the sensitivity of the finger tips accompanied by increased sensitivity to heat. There was a flattening of the normal ridges of the skin, thickening and hardening of the horny layer with scaling and cracking in varying degrees. There was also a curious, marked, failure of the parts to regain their normal shape after pressure had been applied and removed resembling the same characteristics as is seen in cases of pitting edema. There was thickening of the growth of the cuticle at the base of the nails accompanied by brittleness and a tendency to crack on the part of the nails themselves while at the tips of the fingers they tended to stand away from the fleshy part of the fingers.

Carcinoma of the skin following radium burns is much less common than in the case of x-ray injuries although two cases have been fully recorded in the

literature (21).

In summarizing, the effects of radiation upon the skin vary as to the dose used and whether it has been subjected to repeated radiations over a long period of time or to a therapeutic dose such as is given in treating the average case of neoplasm of the breast, cervix or other intra-abdominal or intra-thoracic lesions.

In cases of workers absorbing a great deal of radiation over a long period of time a chronic dermatitis will result as described which is prone to undergo malignant degeneration.

In the therapeutic cases one generally sees a transient erythema coming on two to three days after beginning therapy and disappearing in two to three days. Then in about two to three weeks following the treatment a moderate erythema accompanied by vesiculation with crusting and loss of hair will develop lasting from three to six weeks and then healing will occur rather spontaneously. It is only when large doses have been used that this will persist for a long time, undergo healing and then several months to several years later undergo a late reaction followed by malignant degeneration and the absence of healing in the irradiated area.

b. RETICULO-ENDOTHELIAL SYSTEM

It was in 1904 that Heinke made the first careful histological studies on the blood and blood forming organs. He demonstrated that the lymphoid tissue was primarily affected and noted that degeneration of the lymph follicles in the spleen and a diminution in the number of lymphocytes in the circulating blood developed.

He demonstrated that after sufficient radiation marked leukopenia developed with polymorphonuclear neutrophilic leukocytes predominating in the differential count. He also noted that if sufficient radiation was given over bones there was an aplasia of bone marrow and increased destruction of the white cells over the red marrow cells.

Aubertin and Beaujard in 1908 were the first to report leukocytosis being produced prior to a leukopenia. The leukocytosis is almost always entirely due to polymorphonuclear neutrophilic leukocytes with disappearance in comparative numbers of the lymphocytes.

All observers have found following the leukocytosis there is a decrease of the white blood cells especially the lymphocytes and have noted that leukopenia develops if sufficient irradiation is used. (77)

Taylor and others (114) experimenting on mice noted

a sudden decrease on the circulating lymphocytes immediately following exposure followed by rise then fall then return to normal. X-rays were noted to effect the lymphocytes before any of the other circulating cells. The polymorphonuclear forms increase at first then fall and return to normal before the lymphocytes do. The other cells of the blood follow along the same line.

Thomas and others (115) using dosages of low penetration ($7/8$ inch spark gap) noted in their findings a lymphocytosis followed by a steady return to normal. There was some question as to whether this was due to the direct effect of x-rays or secondary to changes brought about either in the circulating blood or superficial tissues.

Further observations of the effects of x-rays upon lymphocytes causes a marked drop in circulating lymphocytes up to 50% even after one second exposure to x-rays. This lasts for one hour followed by a rise to above normal in four hours with a secondary drop to below normal in six hours with return to normal in 24 hours (107). These findings have been confirmed by others who also found no evidence of a stimulating dose from x-rays or beta rays of radium (81).

The lymphocyte is the most sensitive cell and the change in the numerical relationship of the lymphocytes accompanied by a noticeable change in the total leukocyte count when small dosages are used. (63)

In observing the blood count and blood pressure during the course of high voltage therapy it was noted that the lymphocytes were first involved and showed marked and rapid reduction. The polymorphonuclears increased temporarily followed by rapid diminution. This was followed by gradual regeneration and return to normal. Little if any effect was noted on the red cells. Such changes are not due primarily to the direct effect on the blood forming organs because they take place when the spleen and bones are not irradiated. No change was noted in blood pressure (26).

Mottram (78) agrees with the above descriptions that the small lymphocytes are the most sensitive cells to radiation. In explaining the lymphopenia developing soon after irradiation he notes that the irradiated capillaries show an increased number of lymphocytes hanging on their sides. It is suggested that this is where the cells disappear to account for the lymphopenia in the blood stream. Many of these cells are seen in tissues surrounding these small capillaries. It may be that there is a change in the endothelial cells or

tissue damage which causes the cells to accumulate in these areas as it is known that lymphocytes collect in areas of damaged tissues. At a later period macrophages appear in the area of damaged tissues and it may be that the sticking of the lymphocytes to the endothelial walls of the blood vessels is the first stage in this reaction or that these lymphocytes later turn into macrophages.

The sensitivity of the lymphocyte and the findings of the preceding descriptions were confirmed in the experiments of Latta and Ehlers (60).

Warthin in 1906 investigated the effects of x-rays upon the blood forming organs. He noted that the effects were much less on the bone marrow than upon the spleen or upon the lymph nodes. Single short exposures produced no perceptible effects but longer exposures caused destruction of the cells of the large lymphocytic and myelocytic types. The small lymphocytes did not show the marked disintegration that was found in the spleen. The longer and more intense exposures caused an increase in the number of the degenerating and vacuolating large lymphocytes and myelocytes and a relative increase in the small lymphocytic forms. The disappearance of lymphocytes was preceded by nuclear degeneration (97).

No effects were noted upon the red cells. White cell formation in the bone marrow was undoubtedly inhibited in the marrow immediately after irradiation. He concluded by saying that the destruction of lymphoid tissue is always more marked in the spleen than in the lymph glands or bone marrow. The cells chiefly affected are the large and small lymphocytes and myelocytes, these cells being destroyed in greater numbers than the polymorphonuclears (121).

The spleen after small doses of x-rays (spark gap 7/8 inches, 20 minutes exposure 25 M.A.) remains approximately normal at the end of 24 hours showing only a slight increase in mitotic figures. At the end of 48 hours there is a slight increase in the number of necrotic cells but this is not enough to be considered abnormal. At the end of 4 days the mitotic figures in the germinal centers are decidedly increased. By the 7th, 10th and 14th days the spleen had returned to normal showing only a slight proliferation of lymph cells. In the lymph glands there is an immediate increase in the mitotic figures. In 48 hours more mitoses are seen with a slight increase in degenerating cells mainly in the pulp spaces. In 4 days the mitotic figures were less numerous and at the end of the 7th, 10th and

14th days there was only a slight increase in mitoses (83). He concluded that small doses have a stimulating effect upon the lymphoid elements with lymphocytosis resulting (84, 85)

Levin confirms previously described reports in asserting that the lymphatic structures are the most severely affected or are destroyed by irradiation. Even intense irradiation in any region of the body is followed by a complete or partial destruction of the cellular elements of the lymphoid tissues. (64)

In irradiating guinea pigs and rabbits Lacassagne and Lavedan (51) noted considerable diminution in leukocytes, lymphocytes and blood platelets but an almost unchanged number of large mono-nuclears and erythrocytes.

Histological studies of the spleen following the use of large doses of radium showed that the cells present were almost endothelial and small mono-nuclear in type. The lymphocytes were few in number and when seen usually constituted small foci in the neighborhood of blood vessels. Staining and definition of most nuclei was good but a certain number of degenerated forms were present and there was definite evidence of nuclear debris (75).

It has been shown that the spleen and lymph glands

show identical changes. There is enormous pyknosis of the nuclei in the germ centers and soon afterwards throughout the lymphatic tissue. The phagocytes take up the disintegrated chromatin and in twelve to fourteen hours after irradiation very few cells and phagocytes remain. In twenty-four hours regeneration has taken place if no lethal dose has been applied (98).

The reaction of lymphoid tissue to radiation as demonstrated by irradiation of the popliteal lymph node of a rabbit can be divided into three periods. The early period is during the first twelve hours following irradiation. It is characterized by an increase in size of the lymph node, nuclear disintegration and decomposition of the germinal centers. With this reaction some of the phenomena of inflammation are seen -- cellular infiltration, congestion and exudation. Mitoses are seen during this period when a small dose is used. The middle interval is seen from twelve hours to five days after the irradiation and is characterized by phagocytosis and clearing up of the cellular debris. The late period is seen after the fifth day and is characterized by fibrosis of the lymph node. The degree and rapidity of these phenomena are in proportion to the dose used. On the control

side of the animal the same type of reaction was noted but was much slower and showed less response, otherwise it is the same (1).

In irradiated rabbits the decreased faster than the number of erythrocytes and determinations made it appear probable that the immature erythrocytes of the red bone marrow were injured chiefly as regeneration of erythrocytes was good at first and then failed later (57).

Even when there is no loss of hair or skin reaction there is definitely less hemopoietic tissue in the marrow of epiphyses and ends of the diaphyses than normal (7).

In the bone marrow following small doses of x-rays the nuclei of all white blood cells will show pyknosis beginning first in the lymphocytes. If the dose is large enough only the red blood cells will remain intact within the capillaries of the bone marrow. Regeneration has been demonstrated as possible even after extreme exposures (98).

Martland and his associates (70) have reported one particularly interesting case which serves to illustrate some of the dangers in using and handling radio active substances. This patient was a worker in the watch industry and was in the habit of pointing the brush she

was using to paint the dials in her mouth. She died with symptoms of an acute leukemia. There were purpura present all over her body and marked hemorrhage in the subcutaneous and submucous tissues and even into the viscera. The blood picture shortly before death showed the hemoglobin to be 24% red cell count 1,344,000, white cell count 960 and the differential cell count: polymorphonuclear 52%, lymphocytes 46%, myelocytes 1% and eosinophils 1%. Histologically, the main lesions were confined to the organs of the hemopoietic and hemolytic systems or the reticulo-endothelial system. By use of the electroscope the spleen and bone marrow showed by far the greater amount of radio activity. Both the spleen and bone marrow showed histologic pictures similar to pernicious anemia with the exception that the evidence of destruction of the red cells by the histocytes (hematophages) lining the bone marrow and splenic sinusoids was practically absent and the hemosiderin deposits in the spleen, liver, heart and kidneys was not as pronounced as in the most cases of pernicious anemia. There was an entire replacement of the fatty bone marrow by active regenerated tissue, a marrow of the megaloblastic type. Atrophic malpighian follicles were found in the spleen.

The effect of radioactivity introduced into the

body may be divided into the effect from a single lethal dose and the effect from small often repeated accumulated doses.

The local effect from the single lethal doses in destruction of tissue, while in the case the local effect small repeated doses may be present or absent.

The generalized effect from the single lethal dose is a spontaneous anemia with leukopenia. The generalized effect from small often repeated accumulating doses may be divided into a period of stimulation, period of over-stimulation and period of exhaustion. During the period of stimulation, the erythorytes and leukocytes is increased and the patient is in good health. During the period of over-stimulation, the erythrocytes and leukocytes are still high, the patient is beginning to show a loss of weight and has bone pains and nerve pains which is probably a neuritis. During the period of exhaustion, the body defenses are lowered and may develop one of three clinical conditions. First, the patient may show a rapid progressive leukopenic anemia of the pernicious type with terminal infection; second, the patient may have a chronic leukopenic anemia of the pernicious type with local infection e.g. bone necrosis and third a chronic leukopenic anemia of the pernicious type with death resulting from anemia or terminal

infections.

It is evident from experiments on citrated blood and the exposed jugular vein of a horse that x-rays cause more rapid coagulation (37). Radiation of not only the spleen but of the blood in vivo in any portion of the body causes increased coagulability of the blood as has been shown by placing tourniquet around the arm and irradiating the arm (92).

Prolonged exposure to radium causes a profound fall in the number of blood platelets followed by a return to normal then a rise above normal and finally a return to normal. Repeated small doses to a primary increase which is maintained for a few days and then followed by a return to normal (79).

No change was noted in erythrocyte sedimentation during the process of x-ray irradiation by either filtered or unfiltered irradiation (106).

In summarizing one is led to believe that the lymphocytes are the most sensitive of the cells to irradiation followed in order by the polymorphonuclears, mononuclears, eosinophils, and red blood cells. The hemolytic and hemopoetic tissue are the most sensitive tissues of the body.

c. CIRCULATORY SYSTEM

HEART:

The heart is one of the organs which is not particularly sensitive to radiation, at least with dosages within a therapeutic range. If it were there would be many more reports of damage to it following therapy over the thorax. This does not mean that it cannot be damaged by extreme dosages used for experimental purposes or from secondary changes in its own vessels following repeated doses of therapy.

The first experiments recorded of the effects of radiation on the heart were by Sabrazes and Riviere in 1897 who stated that the tracing of the heart of the frog remained unaffected even by exposure of one hour. (29). Allen in 1903 in his investigations concluded that x-rays tend to inhibit cardiac function in cold blooded animals (2).

Warren and Whipple in 1902 tested the comparative sensitivity of thoracic and abdominal viscera to radiation and noted no clinical or pathological disturbances in the heart of animals irradiated over the thorax (29).

Gordon, Strong and Emery investigated the functional and organic effects of irradiating the precordium of

rabbits. Only in one rabbit was there any variation from the normal. It showed ventricular extrasystoles which stopped following irradiation (44).

Roffs (1924) working with cultures from the embryonic tissue of the heart concluded that the heart muscle is comparatively insensitive to radiation (29).

Swan (112) investigated the immediate functional effect of x-rays on various tissues by exposing the bodies of an unspecified number of cats, guinea pigs and rabbits to unfiltered rays of medium quality for varying periods. He noted a marked and progressive fall in blood pressure which was recorded continuously by a mercury monometer. The heart appeared to beat more vigorously than the normal organ. The respirations were at first increased in depth and frequency but later marked respiratory depression occurred.

These findings were contradicted in 1927 by Stephens and Florey (110) who shielded their animals with an electric screen while Swan did not. They noted no change in blood pressure, cardiac function or respiration.

Davis in 1924 in his experiments testing the action of x-rays on the normal lung noted that in one of the animals the pericardium underwent serofibrinous inflammation and in one other animal the anterior wall of the

right auricle was thickened and numerous petechial hemorrhages were noted in the pericardium and it was thought that these were due to the effect of the x-rays (24).

Fatty degeneration of the heart muscles fibers were the only changes noted by Tsuzuki (117) in his experiments where he exposed the whole bodies of rabbits.

Changes in the heart following 120-280 minutes of deep radiation (200 K.V., 1 mm copper, 1 aluminum filter, 50 cm distance, 30 M A) to the anterior thoracic wall were described by Hartmann, Bolliger, Doub and Smith (49). Grossly there was fluid in the pericardial sac but the pericardium was smooth and glistening and the heart was distended to two or three times its normal size chiefly affecting the right auricle and right ventricle. These changes may have been secondary to the lung changes because on section the lower lobes were almost solid and contained considerable quantities of thin, foamy fluid. Microscopically, interventricular septum disclosed swelling of the striations with an indistinct velvety appearance and irregular staining of the muscle fibers. There was hyperemia of the inter-fibrillar capillaries, occasional extravasations of

blood and moderate infiltration by round and wandering cells. There was an intense polymorphonuclear infiltration of the cardiac muscle. The branches of the auriculo-ventricular bundle were well preserved and showed thinning of the fibrils at the margins of the cells and vacuolization, distortion and shrivelling of the nuclei but no evidence of hemorrhage. The right auricle always showed a hemorrhagic process. There was thrombosis of the tip of the auricular appendage noted in some instances. The valves were always intact. There were areas of homogeneous, pink staining, hyaline degeneration largely replacing the auricular muscle tissue and these areas were surrounded by hemorrhagic infiltration. Some of these muscle fibers appeared as tubular structures filled with vacuoles and suitable staining showed the fibers infiltrated with large and small fat globules. Hemorrhage and hyaline degeneration were not found in the wall of the right and left ventricles or the interventricular septum. Instead there was atrophy of the muscle fibers with indistinct striations and granulation and vacuolization of the cytoplasm of these cells. Many of the fibers were replaced by homogeneous material of a hyaline nature. There was abundant interstitial tissue which was finely granular or vacuolated especially

around the walls of the small blood vessels which were abnormally thickened with narrowed lumen.

Three cases were reported by these men (49) in which changes similar to those just described were seen. However, in two of these the changes could have very easily been due to the disease as the patients were riddled with metastatic deposits, one even showing cardiac metastases. The third case was a mediastinal lymphosarcoma. Grossly, the heart appeared normal but microscopically it showed atrophy of the muscle fibers and increase in the interstitial tissue; and the walls of the arterioles were thickened and surrounded by fibrous tissue. This change in the vessels could very well have been the primary change with the changes in the heart secondary to this.

Warthin and Pohle (123) concluded that a single exposure of the precordium to one H.E.D. (600 'r') of e-rays does not produce definite and irreparable injury to the heart and lungs. In instances where twice this dosage was used, there was an unusual amount of hyaline degeneration without any cause other than irradiation to account for it.

In a later report (124) in which the animals were given an initial dose of 600 'r' and 300 'r' at monthly

intervals for two doses Warthin and Pohle report that all of the animals of this series showed marked myocardial similar but more serious than those previously described. These lesions were associated with a more or less severe bronchitis and broncho-pneumonia.

In 1931 these men (122) noted dilation of the heart grossly and changes similar to those previously described. They concluded the tolerance of the heart was 500 'r' units.

Prime studied the action of radium on the heart muscle of a large number of chick embryos using 150 mgm hours dosage. No great difference was noted between the control and irradiated portions in the primary growth. The tissue was transplanted in forty-eight hour intervals and twenty-four hours after the third generation was transplanted there was marked difference between the control and irradiated portions. Both portions continued to grow but the radiated portion grew more slowly. There was no growth in the radiated portion of the fourth generation although in some instances it continued to pulsate. The controls showed no change between the fifth and ninth generation. These results were regarded by Prime as substantiating Hertwig's view that radium acts chiefly on the nuclear mechanism

of cell division and not on the protoplasm (100).

Fromme concluded that the outstanding effect of radiation on cardiac muscle of cold and warm blooded animals is that of fatty degeneration (29).

Lazarus-Barlow (61) concludes that the striation of cardiac muscle fibers are not affected by short exposures of radium but tend to disappear more and more as the exposure is increased. As the exposure increased or time of survival prolonged the contractile material of the muscle fibers became more finely granular, fibrillated, hyaline, translucent, vacuolated or fragmented. Nuclear vacuolation or vesiculation became common after a long exposure or time of survival after the radiation. The intermuscular spaces were usually wide but contained no adventitious cells except under the most severe conditions when extravasated erythrocytes were found.

Borman (9) sought to ascertain the effect of radon on the sine-auricular node and adjacent cardiac tissue of dogs hoping thereby to obtain information concerning the intimate structure of the node and to determine, if possible, if the node is a more primitive structure than the surrounding cardiac muscle. He concluded that the sine-auricular node was more

sensitive to radiation and therefore more primitive than the surrounding cardiac tissue; that the effect of small doses or the early effect of large doses of radiation is engorgement followed by rupture of the small blood vessels with hemorrhage into the surrounding tissue; that the effects on the sine-auricular node and neighboring tissue are disturbances in circulation, fatty degeneration of cells, disintegration of nuclei, necrosis, proliferation of connective tissue and calcification and that these pathological changes suggest a primary action of radon on the cells and not an action secondary to circulatory disturbances.

These findings were again found in subsequent experiments (8). It was noted that the elastic coat of the arteries displayed resistance to the radiation. After destruction of the node the rhythm simulated was that of normal sinus rhythm.

Clinically, there is little use for x-rays in cardiac disorders.

Levy and Golden (1927) report no evidence of cardiac injury or unfavorable effects in treating cases of rheumatic carditis. In seventeen out of twenty cases, the reported definite improvement of the patient (29).

There was no definite evidence to suggest that x-ray therapy in dosages usually given was sufficient to cause any temporary or permanent changes in the myocardium of patients autopsied, twelve of whom had received therapy over the chest and five in other regions of the body (36).

Animal experiments indicate that the specific radio-sensitivity of the heart is relatively low and that it is able to tolerate large doses of x-rays and radium well beyond the range usually used in treating human beings. Some of the abnormalities noted to appear under experimental conditions appear to be secondary to acute inflammatory changes induced by irradiation in the lungs which are more susceptible than the heart (29).

BLOOD VESSELS:

The action of x-rays and radium upon the blood vessels are similar. So great is the response of the blood vessels to radiation that many observers have considered the therapeutic action of the rays as primarily due to their action on the vascular supply (21)

Degeneration of the vascular endothelium was first recorded by Gassmann in 1899 (21).

Examination of the capillaries shows changes in the endothelium, the cells showing swelling, vacuolation, degeneration and irregular proliferation. Decreased tone of the capillaries has been noted so that a rather quick dilatation took place after radiation thus explaining the casue of redness and edema following radiation (22).

In vessles of larger size, there are the same proliferative and degenerative changes on the interior as in the smaller vessels while the outer parts show leukocytic infiltration and swelling of the collagen fibers. The changes here proceed to obliteration of the vessels, which is usually accompanied by perivascular fibrosis. As a result of the endothelial changes localized thrombosis may occur. Vascular endothelium may be regarded as among the most radio-sensitive of all tissues (21).

Takahashi (113) concluded that young capillaries and fibro-blasts are very sensitive to radiation and that inhibition of healing and capillary takes place when operative wound are irradiated.

Soft beta and gamma rays cause the disappearance of capillaries and a fibrinoid necrosis takes place in the larger vessles. Vessels losing their function are

replaced by connective tissue (32).

References to changes in blood vessels have been made in descriptions of previous tissues. In summarizing the main changes are first a dilatation then a constriction of the vessel finally leading to obliteration. The endothelium is the most sensitive portion of the vessel, and it is here that the earliest and most profound changes are noted. The vasodilation of the vessels is followed by the development of small platelet thrombi in the engorged vessels. They form among groups of leukocytes or radiate from the endothelium of the vessels (101). The vessels in the loose delicate stroma are more readily affected than those in the dense fibrous tissue and collagen.

d. THE RESPIRATORY SYSTEM

NOSE AND ACCESSORY SINUSES

In general the radiosensitivity of the mucous membrane of the nose is uncertain. Experiments on animals to determine the irritability of this structure do not appear to have been made until this last year because aside from tumors little therapeutic work has been reported on this region and because sensitivity to the nose has never been attracted by reports of injury. Many patients irradiated about the face including a part or all of the nose for inflammatory or malignant conditions complain of a loss of sense of smell or peculiar disagreeable odors. From the present knowledge, the sensitivity of the nose does not appear to differ much from that of the mouth.

Meager clinical reports indicate that inflammatory conditions of the nose and accessory sinuses respond to irradiation much as do other inflammatory processes and the mode of action is probably much the same (29).

Heine (50) studied the effects of x-ray and radium upon the ciliated epithelium of the nose and trachea. The changes taking place were hyperplasia, loss of cell outline and the production of pycnotic nuclei, goblet cell formation, and destruction of the epithe-

lium of the nose is not a delicate structure and is able to stand twenty-four erythema doses of x-ray with impunity. He explains this reaction by saying that these cells are an old structure biologically and are therefore the last to be destroyed.

LARYNX

The specific radiosensitiveness of the normal larynx does not appear to have been submitted to an experimental test (29).

On rare occasions injury to the larynx from excessive irradiation have been reported. Hahn in 1919 was probably the first to report laryngeal trouble possibly of several weeks duration after radiation of the neck for cervical adenitis, and also to point out that with very excessive dosage edema of the larynx may result.

Perichondritis of the cartilages of the larynx and necrosis of the hyoid bone and thyroid cartilage have been reported by various men. A review of the literature leads one to believe that the sensitivity of the larynx is not marked.

LUNGS

The first animal experiments of the effects of irradiation on lungs were recorded in 1898 by Bergome

and Tessier who noted the lung and pleura showed much thickening and numerous extrapleural adhesions with retraction of the lungs. They regarded the extensive pleuritis and pneumonitis as the effects of irradiation upon the pleura and lungs.

Wohlauer in 1909 gave $7\frac{1}{2}$ times dose necessary to produce dermatitis to one guinea pig and five times that dose to the second guinea pig. Both of the animals died one and two days later. The lungs of the first showed hyperemia and were studded with punctate hemorrhages. Microscopically the alveoli were filled with albuminous exudate; the peribronchial and perivascular lymph spaces were widely dilated and contained red and white blood cells including eosinophils. The lungs of the second appeared normal grossly but microscopically there was hyperemia, slight exudation into the alveolar spaces and dilation of the perivascular and perilymphatic spaces. The integrity of the alveolar epithelium was thought to indicate that these cells were rather sensitive to x-rays (29)

Davis in his experiments, irradiated the right thorax of two rabbits at intervals of 20, 27, 30 and 104 days respectively killing the animals two weeks after the last irradiation. The left lung appeared

normal but the right showed greatly increased density with the normal markings obscured on cut section. Microscopically there was marked thickening of the alveoli with reduction in size or obliteration of the air space. The alveolar epithelium was normal. There was increased connective tissue surrounding the bronchi and blood vessels. The blood vessels showed considerable thickening, especially the medial layer, in the affected areas (24).

Txuzuki exposed the entire body of rabbits to short x-rays varying the dose from twenty to 100% H.E.P. Strong radiation caused hyperemia, edema and serous exudation into the alveoli but these diminished rapidly and were followed by an increase in the pigment cells. These changes were featured by a degeneration or destruction of the nuclei of the lymphocytes, infiltration of pseudoesinophil cells and hyperemia. This degree of abnormality varied with the dose. Following the administration of 120 to 160% H.E.D. the animals died in an exhausted condition. The lungs showed marked hyperemia, serous and hemorrhagic exudation, into the alveoli with partial atelectosis, desquamation of the epithelium of many bronchioles and alveoli, destruction of the lymphocytes and phagytosis into the peribronchial lymphatic

tissue. There was also infiltration of the interlobular septa with fat or pigment cells and pseudo-eosinophil cells. (117)

Luden and Werthemann undertook to investigate lung changes induced in animals by x-rays with a dosage not so large that it would kill the animals before the changes had time to develop. Their description is probably the most complete. The affected parts were readily seen upon examination. In only two of eleven cases did the pleural cavity contain fibrinous exudate. The affected lobes were gray and showed increased consistency. On section the cut surface was gray and displayed definite pneumonic granulation. The lumen of the bronchi contained yellowish white, sticky, purulent exudate. No organisms were seen in the exudate. Microscopic examination showed that even the lobes which appeared normal superficially presented scattered areas that did not contain air. Some of the interalveolar septa were abnormally thickened and in other areas emphysema had torn the alveolar septa. The capillaries were gorged with leukocytes, adjacent groups of alveoli contained masses of exudate. The alveolar epithelium was sometimes lacking and in some of the lobes where the pathological changes were least pronounced desquamation of

the bronchial epithelium and increased secretion of mucus were noted. The alveolar epithelium sometimes showed vacuolar degeneration of the protoplasm of its cells with occasional swelling or disappearance of the nuclei. The epithelium in the bronchi had undergone a transition to the cuboidal type. Multinucleated giant cells had formed and mitotic division showed an increase. Some of the lungs showed marked purulent bronchitis, bronchiolitis and broncho-pneumonia. (29)

Lazarus-Barlow noted that following short exposures to radium the lungs were congested and filled with exudate and there was alteration of the columnar epithelial lining of the air passages. The capillaries were widely dilated. A few red blood cells and considerable granular debris was found in the alveolar spaces. The nuclei of the endothelial cells lining the alveoli were usually vesicular and faintly stained. After prolonged exposure they were irregularly contracted and deeply stained. Desquamation of the alveolar epithelium was always slight. The columnar epithelium of the bronchi and trachea usually showed degeneration and desquamation sometimes associated with proliferation. The peribronchial lymphoid tissue was remarkable for the absence of lymphocytes the presence of nuclear debris and prominence of

endothelial cells. (61)

Groover, Christie and Merritt (45) were apparently the first to give unmistakable evidence of pulmonary reaction to x-rays when they reported having treated the thorax of a considerable number of patients for carcinoma of the breast. The x-rays were generated at moderate voltage through .5 mm. copper and one mm. of aluminum to the point of deep bronzing, vesication and subsequent desquamation of the skin. Some of the patients developed infiltrative changes of the lungs beginning at the hilus and spreading outward accompanied by dyspnea. The symptoms are those of an irritative, unproductive and usually a paroxysmal cough arising after three or four exposures to x-rays coming on about the same time as the skin inflammation was apparent. Soon after this the radiographic signs of pulmonary infiltration at or near the hilus were seen which spread rapidly until practically the entire lung was involved and this was accompanied by dyspnea. Definite pulmonary fibrosis was seen to remain later in one patient. In other patients the infiltration disappeared without leaving any traces.

Others have reported similar findings. This action did not attract attention until the short wave dosage

came to be used. It has been largely attributed to the fact that doses above skin tolerance have been used in many of these cases. It is believed the essential factor is the quantity and not the quality of the rays that produces the actio (29).

The physical signs are usually limited to one lung and consist of dry and moist rales and a pleural friction rub. Evidence of pulmonary infiltration and sometimes slight pleural effusion may be elicited in the more severe types of reaction (46).

In conclusion the sensitivity of the pleura and lungs is approximately the same as the overlying skin. The mucus secreting cells of the epithelium lining of the bronchi and mucus bronchial glands are more radio-sensitive than other epithelial cells and are the first to react and undergo mucoid degeneration pouring out and increased amount of mucus for a time but later diminishing (29).

e. GASTRO-INTESTINAL SYSTEM

MOUTH

Injury to the mucous membrane of the mouth was noted as early as 1896 in which a patient was having radiographs made of the head to locate a bullet and which resulted in epilation of the scalp, vesiculation of the skin and blistering of the mouth and throat which did not heal for three weeks. The patient being unable to eat solid food during that time. Milder radiation sometimes produces a temporary loss or impairment of taste and of sensibility of the oral mucosa, the degree and duration of which are dependent upon the severity of dosage (21).

It has been noted in dogs that after irradiation the oral mucous membrane of dogs seemed less sensitive to stimulating substances introduced into the mouth. Similar tests on six persons who had received x-ray treatment showed diminished sensitivity of the oral mucosa. The diminution in this sensitivity parallels the diminution of the secretion of the salivary glands after irradiation (14).

The only experiments on animals relating to the action of x-rays and radium on the teeth were performed by Leist in 1925 and 1926 who found that the growth

of the teeth is retarded by inhibiting the development of the odontoblasts and perhaps by also inhibiting growth of the jaw bones. Even mature teeth were found to undergo atrophy and here to as in the growing teeth the odontoblasts were affected (28).

SALIVARY GLANDS

Experiments concerning the effects of x-rays and radium upon the salivary glands have been carried out by Horwitz (28), Lazarus-Barlow (61), Ivy, Arndoff, Jacoby and Whitlow (52), Von Salis (28), Case and Boldyreff (14), and Tsuzuki (117).

The pathological changes as found by these workers agree very favorably and are correlated and discussed in the following paragraphs.

The saliva recovered its normal composition after two to three months showing that the gland cells that are not destroyed recover their full functional capacity. Large doses cause immediate complete suppression of secretion while small doses cause no change in secretion. No gross pathologic results were noted in any of the experiments. The microscopic changes showed a fatty degeneration of the epithelium lining the ducts four days after irradiation followed in 15 to 20 days by infiltration of round

cells about the secretory ducts, blood vessels and in the stroma of the gland. There was a reduction in the amount of mucous in the alveolar cells with some degeneration of these cells and proliferation of fibroblasts into the stroma. After a period of time (two months) there is mucus distension of the alveolar cells, diminution in the size of the gland and increase in its consistency due to connective tissue proliferation (14).

Many writers have noted the sensitivity of the salivary glands clinically, noting that the parotid gland appears to be more sensitive than the sub-maxillary gland and that the glands are much more sensitive than the skin. The unusual sensibility of the salivary glands may be manifested in man by an early, late or combined reactions (62). The early reaction consists in rapid and often marked swelling of the glands following the exposure and reaching a maximum in 12 to 20 hours and subsiding spontaneously in 4 to 72 hours depending on the dose given and also upon the individual, it being said that fair people are more sensitive than dark. There may be slight pain and tenderness but usually there is only the sensation of tension. The cause is unknown for this reaction but it is suggested that it is due

to an accumulation and increase in the specific gravity and viscosity of the saliva in the glands, the excretory ducts of which may be narrowed by cellular swelling or plugged with mucous. The symptoms of these early reactions may be very acute and have often times been diagnosed as mumps. The late reaction is characterized by dryness of the mouth and interference with mastication and deglutition appearing in one to three weeks following irradiation reaching a maximum in two to four weeks and then gradually subsiding. The severity and duration is dependent on the dosage given. The combined reaction is a combination of both the early and late reaction in the same individual.

STOMACH

The earliest systematic work of the effect of radiation upon the stomach is that of Regand, Nogier and Lacassagne in 1912 who carried out a series of experiments on six dogs. In their work, they found that the gastric mucosa of the stomach was not very sensitive to radiation -- the living epithelium of the pylorus and pyloric region showing but little response. The fundus was definitely more sensitive to radiation due to the fact that it is the most

glandular portion. In their experiments it was found of the two types of gland cells that the chief cells undergo degeneration earlier and with less dosage than the parietal cells. The interglandular connective tissue showed extensive leukocytic infiltration (28).

Szego and Rother in 1921 irradiated a dog through a Pavlov giving 38% erythema dose first time, 47% on the seventeenth day, 88% on the forty-seventh day, and 116% on the sixty-first day. They noted a decrease in the total secretion, the total and free HCL, pepsin and rennin values. This was regarded as evidence of injury being followed by a rapid return of the secretion to normal. Following the last irradiation, the dog became dejected and vomited through the fistula. Gross examination showed marked atrophy and numerous petechiae on the mucosa lining of the stomach. Microscopically, the mucosa had lost one half of its thickness and this thinning was also noted in the lamina propria, muscular and submucous coats. Except for scattered rests, the parietal epithelium had disappeared. There was marked proliferation of connective tissue seen in the deep portion of the mucosa giving it a sclerosed appearance. The acinous epithelium was atrophic and some of it had become cystic (28).

Ivy, Orndoff, Jacoby and Whitlow concluded that the

gastric glands are not stimulated by small doses of x-rays, that one and one half times erythema dose causes marked hyposecretion of mucous, marked reduction in pepsin secretion -- it showing reduction before the acid and complete achylia for three weeks returning to normal quality in three to four weeks but being permanently reduced in quantity. These workers state that gastric glands were 40% more sensitive than the salivary glands (53).

Miescher in 1923 found that following first irradiation there was a temporary increase in gastric juice fourteen days after the first irradiation with a return to normal, then subnormal, then a progressive increase to preradiation level or higher (28). This was noted after each irradiation. Pepsin secretion reacted more slowly to radiation always on the downward side with no evidence of stimulation.

Portis and Arens noted that following irradiation over the thorax, shielding the abdomen, there was essentially no effect on the free and total HCL. Exposure over the stomach alone caused an immediate sharp rise in the total and free HCL followed promptly by a gradual decrease to or nearly complete achylia. The decrease in pepsin was not noted until acid had diminished greatly and was not evident until that time (99).

Evidence concluded by the investigations of others shows that radiation of the thorax with the abdomen shielded leads to no change in the gastric secretion (54).

Brocq, Solomon and Oury concluded that the effect of roentgen irradiation on the gastric secretion is to diminish its acidity.

Dawson described the pathologic changes in Pavlov pouches who stated that the changes produced by single large doses or repeated small doses were the same. The changes that took place both histologically are as have been described (25).

It may be then definitely stated that irradiation of the upper abdomen produces temporary and variable reduction in gastric acidity and definite destruction of the mucosa (109) although the digestive glands are fairly resistant to irradiation, and there is no effect on the functional activity without destroying the effect of the glands (15).

Clinically, there are numerous reports that x-rays have been used in the treatment of hyperchlorhydria and hyperchlorhydria associated with ulcer with the effect being longer and more lasting on the cases of simple hyperchlorhydria rather than those associated

with ulcer. The degree and duration of these effects are dependent on the dosage given (28). Clinically, patients will show improvement following moderate treatments -- there being a distinct reduction in gastric hyperacidity (11).

In conclusion, the mucosa lining of the stomach is less sensitive than that of the intestinal mucosa (28).

THE INTESTINE

Krause and Ziegler investigated the action of x-rays on the internal organs of mice, rats, guinea pigs, rabbits, and dogs. After irradiating the whole animals the chief pathologic alterations being noted were destruction of lymphocytes in the spleen, lymph nodes, intestinal lymph follicles and bone marrow, catarrhal inflammation and degeneration in the mucosa of the intestine (28).

Regand, Nogier and Lacassagne carried out extensive researches on dogs. It was found by them that the lesions in the intestine involve chiefly the villi, glands of Lieberkuhn, the lymphoid and connective tissues of the small bowel, and that the epithelium first becomes detached from the villi, the stroma shrunken and the villi finally disappear. The cells of

glands of Lieberkuhn appear most sensitive. The characteristic lesion is one of acute inflammation, with vacuolation and mucoid degeneration of the cells, hyperemia of the mucosa and detachment of the epithelium by a fibrinous exudate which is accompanied by cell infiltration of the stroma. Marked thinning of the intestinal wall may result -- the atrophic changes even involving the muscular coat (28).

Frome in his experiments noted desquamation of the epithelium, destruction and vacuolation of the nuclei and protoplasm of the epithelial cells with a large accumulation of blood pigment in the villi along the course of the vessels and many hemosiderin cells in the stroma (28).

Hall and Whipple irradiated dogs with rays of different qualities and noted that the manifestations appeared suddenly consisting of vomiting, diarrhea, general depression and loss of appetite. The outstanding changes in the gastro-intestinal tracts were most marked in the jejunum with the epithelium of the crypts showing marked degeneration surrounded by large lumps of polymorphonuclears which were present in the mucosa near the basement membrane of the crypts. The tips of villis appeared immune to such reaction (47).

The rate of autolysis of the intestinal epithelium

that had been irradiated appeared to be greatly increased, the secretory crypt epithelium undergoing autolysis first and that of the villi last, while the reverse is true in the autolysis of normal epithelium. The profound functional disturbance of this important intestinal epithelium is believed to be responsible for the clinical abnormalities and intoxication following x-ray treatments (119).

Others who have confirmed the above descriptions of the effects of radiation on the intestine are Martin and Rogers (66), Tsuzuki (117), and Mottram (82).

Mottram's description of the changes taking place is most unique. The first pathologic changes take place forty-eight hours after exposure. There is a great increase of the mucinogen granules occupying clear vacuoles in the cell protoplasm of the epithelium lining the tubular glands. This was not confined to the goblet cells as in the usual formation of mucous, but was found extensively in the columnar cells and represented the first stage of mucoid degeneration and was mainly seen in the cells at the base of the glands. The granules became less numerous after three days but were larger and the hyaline material was more abundant. After four days few mucinogen granules

were seen and the normal goblet cells were absent. The lumen of the glands were free from mucous, the columnar cells stained more faintly and the nuclei were larger and less deeply stained. After five to six days there was little further change and small areas of desquamation were noted occasionally (82).

Numerous cases of injury to the intestine following radiation have been reported -- the most common occurrence of these lesions is following irradiation of neoplasms of the cervix and uterus. Probably the earliest instance of severe lesions of this kind was reported by Franz and Orther in 1917 in a patient with carcinoma of the cervix who had received three courses of therapy developing a diarrhea after each course and at autopsy ulceration and necrotic changes were found in the mucosa.

Many other cases have been cited by various writers. Jones reported seven cases of benign stricture developing eight months to eight years following radiation treatment and explained it on the basis that a loop of bowel comes to lie in the pelvis during treatment and a secondary peritonitis results which keeps it in this same position so that it receives very intense irradiation. Sections of these strictures of the small bowel show marked thickening and dense fibrosis of the serosa in which

there were large numbers of greatly thickened arteries showing varying degrees of obliterative endarteritis, degeneration of the lamina elastica and hyalinization of the intima. In some areas, there was localized perivascular inflammatory infiltration with plasma cells predominating. There was considerable diffuse increase of fibrous tissue in the muscular coat with fibrosis of the submucosa. The mucosa was atrophic, contained little lymphoid tissue and showed mild diffuse inflammatory infiltration with numerous eosinophils and plasma cells present. In one area an ulcer was present and in the area of this ulcer the ganglion cells of the submucosa showed extensive degenerative changes (55).

In summarizing, one must say that after reviewing the findings presented that the small intestine is far more sensitive than the stomach or colon and the duodenum and jejunum are the most sensitive parts of the small intestine and of the cells of the villi also the crypt cells are more sensitive than the tip cells.

PANCREAS

The susceptibility of the pancreas has never been clearly established (28). Experiments on the intact pancreas by Tsuzuki indicate that under normal conditions,

the pancreas is not greatly influenced even by strong irradiation (117) and then there is only slight degeneration of the parenchymatous cells.

Others have shown the pancreas to undergo degenerative changes with fibrosis and very rapid regeneration resulting. Orndoff et al (38, 88). These workers found that three erythema doses causes marked fibrosis of the pancreas with regeneration and that four and five erythema doses causes complete disappearance of the pancreas with diabetes resulting.

It has been found that the beta cells are the most sensitive, the alpha cells less sensitive and the acinar cells the least sensitive of those in the pancreas (12).

A search of the literature for instance of injury to the pancreas directly attributable to the effects of x-rays and radium have been fruitless. This is by itself strong presumptive evidence of the relative resistance of the organ to radiation (28).

LIVER

It has been generally thought that the liver is resistant to radiation, but in 1924 three cases were reported of hepatic lesions occurring in patients treated by deep x-ray irradiation presenting the

following picture: The epithelium of the medium and small sized bile ducts showed vacuolation, swelling and necrosis, attended by slow and atypical degeneration with formation of giant cells blocking the ducts resulting in bile stasis and hemorrhage. Some injury of the hepatic cells at the periphery of the ducts was also noticed but these appeared definitely more resistant than the epithelium of the bile passages (16).

f. REPRODUCTIVE SYSTEM

Before taking up the effects of radiation on the reproductive system it might be well to review very briefly the development of the normal male and female germ-cells.

The primitive gonad arises as a thickening of the mesoderm on the medial side of the urogenital ridge beginning about the sixth week of intra-uterine life at which time there is no differentiation of sex. Sex differentiation begins to show about the seventh week and shows about a week earlier in the testis than in the ovary.

Lying between the cells of the germinal epithelium are larger cells termed the primitive ova which are later carried down into subjacent tissue by budlike ingrowths of the germinal epithelium. These are the genital cords. In many instances the cell masses retain their connection with the germinal epithelium and form cellular columns known as Pflugers tubes. The surface epithelium finally forms the permanent epithelial covering of the ovary and is distinguished from the adjacent glistening peritoneum by its relatively dull appearance.

The adult ovary consists of the germinal epithelium which is a single layer of low cuboidal cells; the tunica albuginea which is a layer of poorly developed

connective tissue capsule consisting of ill-defined interlacing fibers with some cell elements situated beneath the germinal epithelium; the cortex in which the germinal cells lie; and the medulla or central portion containing vessels, nerves, lymphatics and a remnant of epithelial tubes the rete ovarii.

The germinal cells are given different names for each stage of development they happen to be in, in the course of their development of the mature ovum ready for fertilization.

During the early stages of development these germ cells are known as oogonia and repeatedly divide and then the oogonia enlarged are known as the oogonia of the first order. The primary oocyte undergoes a mitotic division whereby the chromosomes are reduced by one half and the first polar body is extruded. The oocyte resulting is the oocyte of the second order and undergoes division and after extrusion of the second polar body the oocyte becomes the ovum.

The first stage in the production of the Graafian follicle is the formation of the primitive follicle. First the oocyte is surrounded by a single layer of flattened cells not separated from the stroma by definite membranes. This occurs in the fifth month of fetal life. These primordial follicles may remain

changed until the menopause, develop into mature Graafian follicles or undergo atresia and disappear.

The first stage in the formation of a Graafian from a primordial follicle is a change in the character of the flattened cells enveloping the oocyte. These cells become cuboidal or cylindrical, multiply by mitoses and form a stratified epithelium known as the membrana granulosa. By the time that this has attained a thickness of three layers of cells changes have taken place in the immediately surrounding ovarian stroma which differentiates into a close fibrillar network called the theca interna. Immediately surrounding this is a zone of interlacing cells, the theca externa.

Some of the cells of the membrana granulosa next undergo vacuolation and a cavity is formed which enlarges and contains liquor folliculi. As the cavity enlarges the oocyte becomes larger undergoing mitosis with the extrusion of the first polar body becomes an oocyte of the second order or ovum. As the Graafian follicles develop they migrate toward the medulla, bulge outwards to the cortical zone pushing the tunica albuginea before them and eventually protrude the ovary. With rupture of the follicle the ovum is discharged and passes along to the uterus.

The testis shows differentiation about one week

before the ovary and in this early stage is characterized by branched and anastomosing strands of cells, the testis cords; and the formation between the covering epithelium and the testis cords of a loose connective tissue layer, which will subsequently become the tunica albuginea.

The primordial germ cells of the testis cords form the early spermatogonia of the semineferous tubules; but the later generations probably arise from the indifferent elements, which also transform into cells of Sertoli.

The male germ cells are in various stages of development and are arranged in layers and after numerous divisions these are spermatogonia. Some then remain as stem-cells while others of the later generations enter upon a period of growth of which the enlarged cells are known as the primary spermatocytes. These then divide into secondary spermatocytes which are equal in size to functional and then each of these divide into two spermatids. During the last two divisions the cells decrease in size and the reduction in chromosomes is reduced one half. Each spermatid then becomes attached to a cell or Sertoli and gradually is transferred into the typical spermatozoa. (21)

The effects of radiation on the ovary were first observed by Bergonie and Tribondeau in 1904 who found that the ova were susceptible to radiation and the primary follicles were more sensitive than the later stages of development of the ova.

Regand and Lacassagne studied irradiated rabbit ovaries and found that the primary follicles degenerated in from 15 hours to 4 days and the oocytes degenerated and underwent absorption about the seventh day. In the older follicles the follicular cells disappeared in from 2 to 4 weeks. The mature follicles showed nuclear degeneration, polar body formation and segmentation. After three months new interstitial tissue was formed from the cortical connective tissue (21).

These results are confirmed by Lacassagne and Coutard (58), Seide (108), Mavor (74), and Funk and Bucker (41).

Histologically the changes seen in the ovary are a round cell infiltration, engorgement of the blood vessels, and extensive fibrosis in and about them throughout the entire organ with more or less disintegration of the follicles depending on the dose administered (72).

It has been shown that irradiation 8 to 14 days after menstruation is more apt to produce

abortion than irradiation 35 days after menstruation and is explained by the fact that at this stage of development cell division is greater and the action of rays is felt more readily by cells of embryonal type. (4)

No degenerative changes have been noted in the follicles of animal ovaries after 600 milligram hours of radiation (73).

Albers-Schonberg was one of the first to notice that male guinea pigs and rabbits were sterilized after irradiation of the abdomen. Temporary sterility following irradiation was noted in 1906 by Villemin.

Microscopically from the 8th day after irradiation the organ becomes less firm and diminishes in volume, the maximum change being observed in one month when the testes is reduced to $2/3$ of its size.

Spermatozoa are noticeably diminished in number at the end of the 30th day and after two months there is complete aspermia.

Three months after irradiation one of two things may have happened varying according to the severity of the dose. Sterility may persist, although the health may remain good and the animal retain its ability to copulate or if the dose is insufficient to cause permanent sterility the testis may return to

normal size and the spermatozoa reappear (21).

The immature testis is more sensitive than the adult gland and the recuperating powers depend on the age of the individual and the dosage given (51).

The spermatogonia are the most sensitive and the spermatozoa the least sensitive to radiation (21).

Much has been written of the effects of radiation upon the reproductive system and the effects produced upon the offspring, but time and space will not allow a complete review of this phase of biological effects here except to state that radiation of the organs of reproduction followed by subsequent pregnancy is apt to lead to the formation of monstrosities and developmental defects passed on to succeeding generations.

g. GENITO-URINARY SYSTEM

KIDNEY AND URETERS

In the course of their observations of the actions of x-rays upon the blood Helber and Linser observed symptoms of nephritis in some of the experimental animals after irradiation (21).

The action of x-rays upon the kidneys of dogs was investigated by Hartman, Bolliger and Doub (48) who obtained definite evidence of nephritis as the result of the exposure. Tremendous doses were given. Changes produced in the kidney were degeneration of the tubular epithelium later replaced by fibrous tissue. Vascular changes were produced and involved all of the vessels from the renal arteries to the capillaries, the vessel walls showing thickening and in some cases definite obliterative endarteritis. In general the glomeruli were well preserved (126)

The final lesion in the kidney is described as a combined type of interstitial and vascular nephritis of extreme grade. In chronic glomerular nephritis as seen in man the glomerular changes are primary but all investigators (28) have noted the reverse in irradiated kidneys, the tubules being primarily involved, this followed by proliferation of connective

tissue, obliteration of the capillaries and finally glomerular atrophy (75).

Others have shown these same changes consistently, (34) and have noted that when x-ray nephritis is well established there is nitrogen retention, acidosis, hypercholesteremia, polyuria uremia and variable amount of edema.

McQuarrie and Whipple noted no change in renal function during the disturbance of a general x-ray intoxication. There was a minimal disturbance of renal function by the use of larger doses, the function being lowered for a few days. These men in their work were unable to recognize any histologic change in the kidneys and noted that the epithelium of the kidney was more resistant than that of the small intestine (66).

The effect of irradiation on the ureter with radium placed along the ureter giving 75 milligram hours leads to constriction of the ureter with secondary hydronephrosis in rabbits and dogs (69).

Many cases have been reported of secondary hydronephrosis in cases of carcinoma of the cervix either due to invasion of the neoplasm or secondary to radiation. So in placing radiation in this region one must remember the ureters may be damaged.

No experimental work is recorded of the effects on the bladder but a word may be said of the effects of radiation in this region. Radiation in this region often produces bladder irritation if the dosage is too heavy or the radium is misplaced along the bladder. The symptoms are burning on urination and frequency often becoming very severe. Sometimes ulceration may result with the formation of vesico-vaginal fistula (21).

ADRENALS

Early animal experiments were carried out by Harvey in 1908 and by Cottenot, Mulon and Zinimern in 1912. Cortical changes are described but there is no mention of changes in the medulla or other organs.

In a dog with one adrenal removed and irradiation to the opposite one the dog became less active one month later showing weakness and loss of appetite. One week later there was marked exhaustion and death (39).

Most animal experiments show changes in the cortex first but it has been shown by some that the medulla is more sensitive than the cortex following heavy doses (104).

Arrillaga and Izzo (5) report a case in which a man was given x-ray treatment for epithelioma of the

tonsil and following this developed an intense suprarenal insufficiency. However, this can be ruled out entirely because of many thousands of cases treated without any reaction.

PARATHYROIDS

Stovin (111) gave 600 to 1500 milligram hours of radium over the thyroid and noted that the parathyroids were not affected in any appreciable manner although the thyroid was greatly reduced.

h. OSSEOUS SYSTEM

BONE

X-rays and radium do not produce any marked effect on adult bone and injuries to this type of tissue is rare even after repeated radiation. This leads one to believe that the bone is very resistant. Only injuries to be noted here are that in some of the early x-ray workers who took no protective measures fragility of the bones of the hand and wrist developed. These bones showed lack of density in the radiographic studies (21).

Necrosis of the bone has been noted in patients treated with radium for malignancies of the jaw and in workers in the industry, those especially prominent were the workers in the dial painting of watches and clocks. Reports of these incidences have been given by Martland, Harrison, Conlin and Knief (70), Phemister (95), and Flinn (40).

Flinn reported two cases associated with industry with fracture of a spontaneous nature. The first case showed delayed union of the fracture with cataract formation in both eyes. In the second case the first fracture took place eleven years after leaving the industry and the second fracture one year later direct-

ly above the site of the first fracture in the right femur. Radiographically the bone was distinctly softer than normal due in part to disuse and in part to the action of the absorbed radium. Flinn also reported two cases of bone sarcoma arising in workers long after their exposure. Autopsy reports of two cases who showed moth-eaten areas throughout the skull radiographically. Microscopic examination of these areas showed areas consisting of loose fibrous connective tissue with only small islands of bone in them. There was marked irregularity of bone along the lesions. The connective tissue was rather acellular. About the blood vessels occasional myeloid foci and lymphocytes along with scatter hemorrhages were seen.

The same findings were seen in the second case. It was concluded that this was the result of deposited radium and was due to the striking of the alpha particles on a nucleus of a bone cell. Probably 98% of the emanation is carried in the blood stream and excreted in the lungs.

Phemister's report only adds that the action on bone is similar to that on other tissues and when allowed to go on long enough necrosis will result. The necrosis is replaced by a slow growth of bone due to the fact that the tissues in and about this

bone had also undergone radium necrosis. In order for this slow replacement to take place it must remain free from infection.

Martland (71) has reported 5 cases of bone sarcoma, pathological fractures, acute anemias and bone necrosis similar to those described in workers.

The effect of radiation on growing bone is much different and in 1903 Perthes noted that growth in the wing of a one day old chicken was greatly reduced.

Brooks and Hillstrom (10) noted that doses over a 40% skin erythema dose cause an inhibition of growth in young animals. It was also noted that bone regeneration and repair were retarded after a subperiosteal resection following 100% S.E.D.

Wilkins and Regen (125, 102) investigating the effects of x-rays on growth and phosphatase activity of bone exposed the fore-foot and leg of 41 pups giving 100 'r' and killing them in three to thirty four days after irradiation. The influence upon the phosphatase activity as compared with the controls showed a decrease beginning in a few days after exposure, reaching a minimum in 1 to 3 weeks and showing a tendency to recovery in 4 to 5 weeks. There was a retardation of growth as judged by both the weight and length of the bone.

In investigating the influence of x-rays on the rate of healing of fractures and phosphatase activity of the callus of adult bone, Regen and Wilkens (103) found that moderate doses of x-rays given previously to fracture in an adult rabbit results in marked delay of union and callus formation; and an inhibition of the use of phosphatase activity that normally accompanies the healing of a fracture.

In a series of experiments using rabbits three to five weeks old Bisgard and Hunt (7) found that growth of bone was not influenced by radiation of the shaft with 1540 'r'. Histologically the epiphysis and new formed bone were essentially normal.

In determining the minimum dosage to provoke growth retardation 400 'r', 300 'r' and 200 'r' were given over the epiphysis. No gross disturbance in growth was noted in the 300 'r' or 200 'r' rabbits. The 400 'r' rabbit showed 5 millimeter shortening in 167 days after treatment. Histologically the discs varied greatly in thickness separating the epiphysis to diaphysis in some areas by a very thin layer. The minimum dose causing histologic change in the cartilage is between 100 'r' and 200 'r' as shown by these experiments. 100 'r' did produce some insult to the

hemipoetic tissue thus showing that this cartilage is slightly less sensitive than the hemopoietic tissue. Histological changes in the rabbit receiving 300 'r' showed the cartilagenous disc to be thinner than normal but distorted and in others there was no suggestion of columnar arrangement. The cells varied greatly in size some being abnormally large and in many the nuclei stained poorly and appeared to be shrunken. In areas where the columns were partially retained there was an abnormal number of empty lacunae and the intercellular matrix was diminished.

The growth of bone in animals receiving large doses was retarded but was never completely stopped until epiphysis disappeared. Epiphysis in irradiated bone disappeared earlier than in non-irradiated bone.

Two cases were reported one of a girl five years of age who had been treated previously for a nevus on the dorsum of the right index finger with radium which failed to grow afterwards, and the other in a boy 17 who had been treated 12 years previously by x-ray and radium on the mesial aspect of the lower left femur with resultant shortening. There was a varus deformity because of continued growth of bone on the lateral epiphysis.

From these reports one concludes that adult

bone is very resistant to x-rays and that young bone is sensitive only at the bone-growing centers. Therefore, when using x-rays or radium in young individuals one must always keep this in mind and not cause any injury if possible.

THE NERVOUS SYSTEM

Danyz was the first worker to study the effect of radium upon the tissues of the central nervous system in 1903. He used one-tenth of a gram of radium salt over the spine and skull of a mouse one month old placed beneath the skin. In three hours, the mouse developed ataxia, in seven hours, convulsions, and died at the end of eighteen hours. In mice that were one year old, similar symptoms developed, but they lived six to ten days. In three guinea pigs where the tube of radium was placed over the lumbar spine there developed a paralysis of the posterior part of the body in one to three days with convulsions occurring a few days later. In the adult guinea pig and rabbits, no nervous lesions developed from the use of radium over the lumbar region. (93). Heinke in 1903 had similar results to those of Danyz and stated that deep hemorrhagic softening spread from the spot at which the radium tube had been applied. Okada in 1905 used radium on the sciatic nerves of young rabbits and noted strong tissue reactions but no alteration in the nerves. Obersteimer in 1905 used 10-50 mgm of radium bromide on the brains of white mice and concluded there were no specific effects on the nervous tissues and that the derangements

that occurred might be accounted for by the destruction of the small blood vessels which resulted in considerable hemorrhage in the brain substance. Horsely and Finzi in 1911 used 110 milligrams of radium bromide in three areas of the brain for two and one-half hours and noted no disturbance in the nerve cells but did note an endothelial proliferation of the walls of the blood vessels of the meninges and punctiform hemorrhages in the cortex and it was their conclusion that no influence was exerted on the nerve tissue. (6)

In his experiments with dogs, Pendergras found that dogs receiving 1150 milligrams hours of radium or less showed no clinical signs of brain damage. All dogs that received 1400 milligrams hours or more of radium radiation died with the exception of one that had received 2500 milligrams hours. The gross lesions of these animals varied greatly depending on the dosage of radiation and the time elapsing since the radiation was given until the examination was made. The dogs that were given doses of 2300-2600 milligrams hours and living eleven days or less presented a dark reddish brown apparently sharply circumscribed oval area on the surface of the brain studded with bright red dots suggestive of petechial hemorrhages. In the dog killed

forty nine days after receiving 1150 milligrams hours of radiation, there was a yellow area, and in the center of this area, there was an excavation showing an irregular jagged base and margins. Sections of the brain of this animal showed necrosis twelve millimeters into the brain substance with small punctate hemorrhages as far into the substance as the internal capsule. Histological changes noted were an endothelial proliferation of the intima coat of the blood vessels, perivascular infiltration, petechial hemorrhage into the brain substance and degeneration of the nerve cells and fibers.

(93)

Bagg in his studies studied the effect of radium emanation on the brain using small amounts of unfiltered and comparatively large amounts of filtered and unfiltered radium inserted into the brain and the effect of a large amount of externally placed heavily filtered radium emanation. In the instance where 127 millicurie-hours was given over a period of thirty days, the examination of the irradiated areas showed an area of necrosis of five millimeters in diameter, surrounded by a zone two to three millimeters wide showing the brain cells in varying stages of degeneration. There was a pronounced leukocytic infiltration tending to wall off the

necrotic area and outside of this there was a broad area showing hyperemia and some pial edema. The ganglion cells near the necrotic zone showed degeneration and all of the nuclei stained poorly. There was some minute blood extravasations with some increase in the small compact nuclei in this area and the pia showed marked round cell infiltration. There was marked perivascular and pericellular edema in the irradiated area. In this instance, there was no neurological disturbances.

Doses of 127 millicurie-hours of unfiltered radium emanation in one-half hour produced a more intensive and extensive tissue reaction with the dog living only four days and developing a progressive left sided hemiplegia. Gross examination showed a large, well circumscribed hemorrhagic lesion 17x18 millimeters involving a large portion of the right thalamus. Microscopic examination showed a central area of brain softening ten millimeters in diameter with extravasated blood throughout the softened area. The blood vessels in this area were thrombosed and their walls were necrotic. There was an area of leukocytic infiltration about the lesion and a zone of degenerated nerve tissue while the ganglion cells for a considerable distance beyond this area showed a loss of chromatin

bodies. The same dosage filtered through one millimeter of platinum caused no apparent neurological disturbances and formed only a small lesion three millimeters in diameter. Microscopic changes were much less intense than in the preceding case. There was only a small area of softened brain tissue with an accumulation of some blood pigment and a few foreign body giant cells surrounded by a new growth of spine cells. The whole section had a cicatricial appearance. About this area were many perivascular lymphocytes and plasma cells.

The effect on the brain of radiating the brain with an external application of heavily filtered radium emanation. An area 20x40 millimeters five millimeters distance over the left cerebral hemisphere was irradiated giving 4000 millicurie-hours in two hours and twenty-five minutes. Fourteen days after the treatment there was a moderate radiodermatitis. There was no neurological symptoms after one month. Gross examination of the brain showed slight congestion of the cortical blood vessels. Microscopic showed no changes either in the brain substance or pia mater. There were two three layer cells surrounding the blood vessels in the sub-cortical fiber tracts and there was a little blood in some of the perivascular lymph sheaths.

In one month after the administration of 9000 millicurie-hours at a distance of 50 millimeters, there were no neurological disturbances and only a slight loss of hair from the left side of the dog's head. There were no gross changes in the brain and microscopically there was increased pericellular nuclei in the gray matter and slight increase perivascular nuclei.

There were no clinical symptoms following the administration of 12030 millicurie-hours, ten millimeters distance. The dog died from a radium burn on the thirty-third day. Grossly, the brain was apparently normal except for a certain amount of anemia of the smaller cortical blood vessels of the left temporal region. No definite degenerative changes were noted microscopically. (6).

Investigating the effect of radium emanation on the corpus striatum no changes other than those described were found after 132 millicurie-hours of radiation. No degenerative lesions were noted in the cord (35).

Davis and Cutler noted no neurological symptoms of brain damage after the use of 864 milligrams hours of interstitial radiation to the brain. They found grossly that the left side of the brain which was the area radiated was slightly more hyperemic than normal.

Microscopic changes were similar to those previously described. The nerve cells in the immediate vicinity of the needle tract showed some demyelination and decrease in size. There was little evidence of nerve death (23).

It is believed by some that radiation does affect the activity of the cerebral hemispheres apparently causing an inhibitory condition. Epileptoid fits have been noted several weeks after treatment followed by general convulsions and foaming at the mouth resembling epilepsy in man. In order to bring about microscopic changes in the brain from roentgen rays, one must wait for several months after the exposure. It is believed the changes in the brain are secondary to blood vessel changes (86 & 87).

Two effects have been noted appearing two to thirty days following the application of 3000-4000 milligrams hours of radium to a nerve. First there was noted a local atrophy at the site of radiation with secondary Wallerian degeneration in the nerve trunk. The local atrophy was shown by disintegration of the myelin into fatty droplets with subsequent disappearance of the fatty droplets. The nuclei of the neurilemma were less distinct and there was no evidence of regeneration

of the nerve after sixty-three days. Second, it was noted that with small doses degeneration of the myelin sheath alone is noted and that there is a great proliferation of nuclei of the neurilemma at the side of radiation (43).

In some instances it has been found that some damage occurs to the nerve sheaths from radiation but that the nerve fibers themselves withstood large amounts of radiation. Even in the presence of radium there was a proliferation of astrocytes. The first changes noted in the irradiated area would always be one of leukocytic infiltration following a proliferation of the endothelial lining of the blood vessels. (13)

Peyton used radium extradurally around the spinal cord in doses varying from 216-806 millicurie-hours. With the small doses, he noted meningeal reaction over a localized area at the site of implantation characterized by leukocytic infiltration, nerve cell injury and proliferation of the glial tissue. With larger doses it was noted that there was nerve cell destruction, myelin degeneration, hemorrhage, focal necrosis of the white matter and fragmentation of the grey matter. The maximum dose of extra dural radium tolerated by the cord in these experiments on dogs was 216 millicurie-hours. (94)

Changes found in the nerve tissue of man are similar to those that have just been described. These were shown by microscopic studies on a series of cases -- two in which the cerebrum was irradiated and five in which the cerebellum was irradiated. (3)

In reviewing the literature, one is lead to believe that nerve thissue is probably one of the most resistant tissues to radiation that is known and it is broken down only when it is subjected to large doses of radiation far greater than is ever used therapeutically. Also one must conclude from the findings that a great deal of the change that is found is due to impaired nourishment of the cells following blood vessel damage.

EYE AND EAR

Complaints referable to the eye were prominent among the first recorded ill effects resulting from exposure to x-rays ranking second only to the skin which has been previously discussed. Soreness and redness of the eyes were described by Edison as early as February 1896.

It was Chalupecky in 1897 who first studied experimentally the effects of radiation upon the eye. He irradiated the right eye of a rabbit forty-five minutes and two hours every other day for eighteen

sessions giving a total dose of twenty-four hours irradiation and it was his conclusion that x-rays cause severe destructive changes especially in the cornea, conjunctiva and iris.

Schulz in 1902 exposed the open eye of a rabbit ten times for fifteen minutes each at a distance of fifteen centimeters and after four to five weeks noted complete necrosis of the skin around the eye but aside from this conjunctivitis he noted no abnormalities of the eye or visual disturbances.

Baemann and Linser in their experiments in 1904 reported no untoward symptoms (27).

Birsch-Hirschfeld in 1904 seems to have performed the first most complete studies on the eye giving a detailed histological description of his findings. In the first rabbit there were no changes until the end of the sixteenth day at which time a conjunctivitis appeared which became increasingly worse for several days, accompanied by a muco-purulent secretion containing desquamated epithelium and an abundance of pus cells. Associated with this there was contraction of the pupil; bleaching and hyperemia of the iris; diffuse haziness of the cornea involving the deeper layers and appearing as an interstitial keratitis. Microscopically

there was marked thickening of the eyelid; pronounced leukocytic infiltration beneath the epithelium extending to the muscular fibers of the orbicularis; thinning of the epidermis with deficient staining and vacuolization of the cells; irregular necrosis of the epithelium; slight signs of atrophy in the muscle fibers where leukocytic infiltration had extended between the bundles; absence of hair follicles; marked perivascular infiltration and endothelial degeneration of the vessels with irregularity of the endothelium resulting from vacuolization, loosening or proliferation of its cells. The conjunctiva showed considerable irregular degeneration and desquamation of the epithelium. There was marked leukocytic infiltration in the region of the limbus especially around the hyperemic vessels. In the anterior layers of the cornea there was necrosis and desquamation of the epithelium which was reduced in places to a single layer of cells with elongated nuclei; marked swelling of the epithelial cells including the basal cells around the periphery of the cornea. There was an increase in mitotic figures and dilated interstitial spaces with leukocytes containing lobulated nuclei and distended or shrivelled corneal corpuscles in the substantia propria especially near the periphery.

The deeper layers of the cornea appeared normal except for occasional foci of infiltration newly formed in the marginal areas. The zone of degeneration was sharply limited. Descemet's membrane was normal. The anterior chamber was filled with an acidophile mass containing a few leukocytes attached as a fine precipitate to the posterior wall of the cornea. The iris showed hyperemia and some thickening of the intima of some of the vessels; swelling of the epithelium of the ciliary body and marked hyperemia of the processes. The lens was clear and the capsule was normal in appearance as was the vitreous. There were slight changes in the retina and many of the ganglion cells were unaffected. The choroid was hyperemic but the walls of the blood vessels were normal and there was no leukocytic infiltration around them. There was no evidence of change in the optic nerve (27). In the second rabbit the changes were the same as have just been described except that there was marked enlargement of the perivascular space; disappearance of the chromatin granules and irregular shrivelling of the nuclei; loosening of the nerve fibers and inner plexiform layers and scant signs of granular disintegration of the outer segment of rods and cones. The pigment epithelium was normal and the choroid was hyperemic.

The optic nerve showed uniform myelin degeneration but there was no particular increase in the connective tissue and glial nuclei. (27)

In the third rabbit which was given a smaller dose there were no changes except for a slight change in the epithelium of the cornea and posterior pigment layer of the iris which was partly destroyed. (27)

The fourth rabbit was a slightly larger dose and showed some inflammatory changes in the anterior chamber that were relatively slight or had completely subsided while in the posterior chamber the degeneration of the ganglion cells of the retina was so pronounced as to lead the partial but marked atrophy of the optic nerve. (27)

Tribondeau and Recamier in 1905 first studied the influence of x-rays on the development of the retina in young kittens. The palpebral fissures of the irradiated kittens opened two days earlier than the control. The irradiated eye remained smaller than the control and at necropsy one month later there was diminished weight of the eyeball. Microscopic examination showed almost complete granular and vacuolar degeneration of the lens; marked fibrillary structure of the vitreous humor; normal development

of the layer of rods and cones; atrophy of the internal granular layer; intensive proliferation of the external granular layer; thickening of the layer of nerve fibers but normal appearance of the optic nerve itself. These men concluded that the effect of x-rays lead to retarded development of the eye, and structural anomalies in the retina, but no affect on the layer of rods and cones; cataract formation and delay in development of the facial bones and teeth (27).

Belley in 1907 irradiated small kittens with x-rays and noted that the exposed eye opened sooner than the other and that the conjunctiva was more sensitive than the skin on the lids. There was a transitory haziness of the cornea characterized by irregular and increased staining of the nuclei and irregularity and thickness of the anterior and basal layers of epithelial cells and some retardation in the pigment formation in the iris. No changes were found in the choroid and in only two instances there was clouding of the Vitreous and aqueous. Degeneration and cataract formation were found in the lens in all but one animal even in those killed fifteen and twenty-three days after irradiation. This degeneration started at the periphery and extended toward the center of the lens. Clinically the change in the lens

could not be noted until 33 days after irradiation but microscopically it was present much earlier as a zone of small vesicles around the marginal portion of the lens with the entire lens becoming opaque later. No inflammatory or degenerative changes were observed in the retina of any of the animals. The only abnormality consisted in a curious malformation characterized by multiple folds of the anterior $1/2$ or $2/3$ of the external granular layer of rods and cones giving these layers a plicated appearance as if these normally developing layers had been made to assume a sinuous form by failure or retardation of development of the coats external or internal to them. This formation was most pronounced in the region behind the ora serrata where the full thickness of the retina begins (27).

Tribondeau and Belley in 1907 noted that only small doses of irradiation were necessary to produce cataract formation which began either at the periphery or the equator of the lens appearing as an annular cloudy zone composed of many small confluent vesicles with the whole lens later becoming opaque showing atrophy and increase in depth of the anterior chamber. Microscopically the epithelium on the anterior surface

was affected first with the crystalline fibers and capsule remaining normal. Changes in the crystalline fibers soon occurred in the equatorial region of the lens, these fibers becoming swollen and their normal finely serrated margins then appeared in sinuous lines. The discrete vacuoles gradually became confluent and formed wide granular plaques. These changes spread rapidly throughout the lens with only small groups of recognizable fibers remaining. Later the anterior portion showed patches of epithelial desquamation separated by areas of cellular proliferation. The capsule remained unaffected for a long time but finally became involved. These workers concluded that cataract formation was directly due to the direct effect of x-rays on the developing epithelium of the lens; that the outer coats were probably affected to a greater degree and more rapidly than the retina, the anterior portion of which continued to grow and arrange itself in folds; and that the exposed eye grew less rapidly than the unexposed eye (27).

Tribondeau and Lafargue noted no effect on any of the structures of adult rabbits eyes after irradiation. They noted that in the kittens one month after the separation of the lids that there was cataract formation

but no changes in the lens in the eyes irradiated two months after the separation of the eyelids and concluded that the radiosensitiveness of the lens diminishes rapidly and the lens soon acquires great resistance to the rays as the animal becomes older.

Bossuet investigated the action of roentgen rays on fetal, newborn and adult guinea pigs, rabbits and dogs. Microscopically and grossly the changes observed in the eye varied little from those just described. He concluded that x-rays may injure mature as well as the growing lens of young animals, the effect being greater on the latter. He explained the greatest destruction which takes place in the equatorial and posterior cortical regions as due to the presence in these regions of the youngest and most rapidly growing cells and the cellular proliferation that takes place in the lenticular epithelium as a compensatory attempt at regeneration.

Rollet and Malot in their work in 1914 noted no changes taking place either in the anterior or posterior segments of the eye.

Froge in the report of his work in 1922 concluded that there was retarded development of the eye as a whole when young eyes were irradiated the degenerative changes present in the lens lead to cataract formation. The

adult lens was not so sensitive to radiation.

Rados and Schinz in the same year reported used irradiation varying from 1/2 to 26 H.E.D. and found no evidence of injury to the lens or retina and no deviation from the normal microscopically. They concluded that the eye was comparatively insensitive and that the danger of cataract formation being induced is very slight.

Jacoby in 1924 investigated the ability of the cornea and retina to tolerate, hard, filtered roentgen rays. His studies of tissue differed not particularly from those previously described. He noted no changes in the lens. The corneal epithelium was the most sensitive of the structures of the eye presenting irregularities in cellular arrangement especially of the basal cells and a variation in the number of layers. The retina showed some scattered degeneration of the ganglion cells and beginning degeneration of the inner granular layers. He concluded the dose necessary to injure the cornea was about 250% H.E.D. (27).

Birsh-Hirschfeld in 1904 tested the effect of radium upon the eye of one young and four adult rabbits and noted that the cellular changes taking place were similar to those caused by roentgen rays. In none of his experiments was he able to demonstrate changes in the lens and the degenerative changes in the retina were not specific (27).

Milroy in 1905 placed radium over an egg to determine if there was any hindrance in the development of the eye or any alteration in any of the other tissues. He noted that the retina was much thinner than normal and the thinning appeared to be due to degeneration of the protoplasm of all the cells of the retina. The lens and muscle fibers are affected the least (76).

London in 1906 noted slight alteration in the cornea and lens. The eye also showed marked central retinitis and neuritis.

Zelenkovsky in 1908 concluded that the radio-sensitivity proportional to the quantity of radium and its length of action. The changes noted in the eye were similar to those that have been described.

Chalpecky in 1911 noted irregularity of the corneal layers with small doses of radium.

Meisner in 1924 concluded that radium produces cataract degeneration and degeneration of the ganglion cells of the retina and medullary sheaths of the optic nerve. (27)

Jonquieres in 1922 noted that the eye can tolerate enormous dosages of radium with no ill effect noted after five years observation. The only change

noted in his experience was some congestion which disappeared in a week or two (56).

Martin in 1933 noted that the conjunctiva in the early stages of reaction was edematous accompanied by hyperemia beginning after a few hours and reaching a maximum in five or six days. Later the conjunctiva will show scarring and shrinking. Edema and ulceration of the cornea were believed by him to be due to secondary changes in the conjunctiva. The lens showed irradiation cataract either as an early or late reaction. There was no clinical evidence to show that the retina was damaged. (67)

The first report in the English literature was reported in 1908 by Paton who treated a patient for lupus erythematosus of the face with the patient noting demness of vision that appeared nine months later.

In 1911 Stock reported a case of triplets delivered prematurely of a woman as a result of x-ray. The lens of each fetus showed signs of cortical degeneration.

Jess reported two cases of posterior cortical cataract three years after treatment for naso-pharyngeal and pituitary tumor. He concluded there is disturbance of nutrition in the lens and as a result of this, chemical reactions take place leading to coagulation

of the lens proteins. In the development of cataract, there is the formation of vacuoles in the posterior cortex secondary to changes in the capillaries of the ciliary body followed by the appearance of fine spots and feathery lines rather cloudy in outline with new vacuoles extending further forward and the posterior portion becoming more opaque especially in the central posterior region. The cataract may develop one to six years after radiation, and one course of deep x-ray therapy is sufficient to bring about cataract formation.

Recent work has shown that the limit of tolerance of the lens is only slightly greater than the conjunctiva with cataract formation appearing in from three months to two years after irradiation (27).

In conclusion one is led to believe from the findings discussed here that the conjunctiva, eyelids, cornea, iris and lens are the most susceptible ocular structures to the effect of x-ray and radium; the conjunctiva and lens being most susceptible, the cornea being more resistant than the lens. The lens is very susceptible to the effect of the rays being slightly more so in the young individual than in the adult. Cataract formation due to the effect of radiation takes place in the posterior cortical region while the formation

occurring with senility generally takes place in the anterior region. The retina in the young is more susceptible than in the adult in which it is very resistant, large doses several times greater than those therapeutically used being required to cause any damage. Only slight changes were noted in the aqueous and vitreous and these are interpreted as being secondary to any inflammatory changes which might be present.

In using x-ray or radium in the vicinity of the eye, one must remember to shield the eye adequately as the danger of cataract formation from the therapeutic dose of x-rays or radium is very great -- the adult lens being only slightly more resistant than is found in young individuals.

Little experimental work has been carried out as to the effects of x-ray and radium on the ear, probably because no damage has ever been noted in humans of damage to the organ of hearing.

Ewald in 1905 introduced radium into the bony labyrinth and concluded that the disturbances produced were similar to those produced by removing the labyrinth which are characterized by turning of the head and toppling toward the affected side.

The experiments of Marx in 1909, Chilow in 1927

and Thielmann in 1928 were inconclusive as to the effects of radiation on the ear (27).

In conclusion, radiation produces no effect on the ear and the changes produced experimentally are consistent with those of trauma in introducing the applicators.

5. CONCLUSIONS

RADIOSENSITIVITY

The effects of radiation upon tissues vary to a very great degree depending on the type of tissue that it is, as one can conclude from a review of the literature.

Many hypotheses have been evolved concerning the gradations of the effects of radiation on the various tissues. Two of the most common are the Law of Bergonie and Tribondeau which states that the effects on the various tissues are proportional to their resemblance to embryonic tissues; and the theory of Regand which explains the effects of radiation to be proportional to the momentary metabolism taking place in the cell at the time it is irradiated. This theory agrees with the theory that the greatest effects are manifested during mitotic division as it is at that time that metabolism is at its height (116).

Interpreting the Law of Bergonie and Tribondeau one is lead to the conclusion that the younger or immature cells are more radiosensitive than the older or adult cells and this theory has long been regarded as the essential foundation of x-ray therapy. The tissues of an individual become less sensitive as the

individual grows older. Although the factors for cell specificity have not been determined, the sensitivity peculiar to each kind of cell seems to be related to the life cycle.

For example the lymphocytes have the shortest life cycle and are the most sensitive while the nerve cells which have the longest life cycle are the least sensitive to radiation (31).

Following is an outline of the various cells and tissues as to their relative sensitivity:

1. Lymphoid cells (Lymphocytes).
2. Polymorphonuclear and esinophilic leukocytes.
3. Epithelial cells.
 1. Basal epithelium of certain secretory glands especially the salivary.
 2. Basal epithelium of testis and ovary (gonial tissues).
 3. Basal epithelium of skin mucous membranes, and certain organs such as the stomach and small intestines.
 4. Alveolar epithelium of the lungs and epithelium lining the bile ducts.
 5. Epithelium of the kidney tubules.
4. Endothelial cells of blood vessels, pleura and peritoneum.
5. Connective tissue cells.
6. Muscle cells.
7. Bone cells.
8. Nerve cells.

The lymphocytes in the circulating blood are thought to be equally as sensitive as those in the spleen, lymph nodes, lymph follicles of the intestines, thymus etc.

The epithelium of certain secretory glands especially the salivary is slightly more sensitive than the polymorphonuclear and eosinophilic leukocytes because there is a reaction on the salivary cells in three to six hours and is not noted on polymorphonuclear and eosinophilia leukocytes until after six hours.

The spermatogonial cells are relatively sensitive while the spermatocytes of the first and second order as well as the spermatids are distinctly more resistant and are affected only by larger doses.

The oogonia are very sensitive while the oocytes of the first and second order are definitely more resistant. In the older ova the follicles are more sensitive than the ova, the older the follicle the more sensitive it becomes. In the primordial follicles the rays act sooner on the ova than on the follicular epithelium of the structures of the skin. The epithelium of the hair follicles is the most sensitive structure and it is seen that one of the earliest effects on the skin is the falling of the hair (31).

Muscle cells are not sensitive with ordinary

therapeutic doses of radiation but pathological changes such as fatty degeneration secondary to other factors such as change in blood supply or cellular intoxication are sometimes seen.

Changes in the brain following irradiation are secondary to changes in the blood vessels resulting in poor nutrition of the nerve cells (31).

RADIATION SICKNESS

X-ray sickness or x-ray intoxication will be included briefly as one of the effects of radiation, the cause of which is unknown but for which many theories have been advanced.

Acute constitutional symptoms of a severe nature became more prominent after the introduction of deep x-ray therapy in which massive dosages were given into the deep tissues without injury to the skin by the cross-fire method.

The onset of post-radiation symptoms whether mild or severe may be rapid or be delayed for days.

Mild symptoms of radiation sickness are malaise, headache, giddiness, faintness, loss of appetite, nausea, salivation, vomiting and sometimes fever and chills which may begin immediately or an hour after radiation and pass off in 12 to 48 hours.

An interesting personal account of recurrent subacute symptoms appearing after a latent period of about three weeks and apparently due to abdominal irradiation is that of Dr. A. E. Barclay.

After 12 weeks work and much fluoroscopic examination with inadequate protection during the war, he began to have painless attacks of profuse diarrhea, at first other symptoms but later associated with initial malaise, nausea, vomiting and on a few occasions the passage of intestinal casts. After ceasing to work the symptoms passed off in three weeks. On returning to work there was an attack 20 days later and this same set of symptoms was established on eight other occasions. Freedom from attacks followed proper protection.

The symptoms of the severe form of x-ray sickness are nausea, uncontrollable vomiting, sometimes with blood, offensive diarrhea, abdominal pain and distension with fever ranging up to 104 degrees, restlessness, profound prostration, progressive cardiac failure, small rapid pulse and dyspnea. When death ensues it usually takes place on the fourth day.

The causes set forth for the milder symptoms are poor ventilation with the presence of nitrous oxide and ozone in the air; high electrical charging of the patient, hemoclastic shock due to destruction of leukocytes; and psychological factors to some extent.

The causes of the late symptoms may be due in part to the causes stated for the mild reaction. Rolleston (105) in his review also adds that the causes may be

an acute toxemia due to the cellular destruction following irradiation, there being an increased protein metabolism; and an acute destructive lesion of the mucous membrane of the small intestine, may be entirely responsible for a non-specific toxemia. Damage to the intestinal mucosa has been given as the cause of intoxication in man, but this is not the sole cause as sickness may follow irradiation elsewhere. Acidosis, alkalosis and changes in the distribution of chlorides in the body have been noted following irradiation. Anaphylaxis has also been given as one of the causes.

In conclusion a number of factors may be combined to produce radiation sickness - flooding of the circulation with the products of cellular disintegration and their action on the central nervous system and the body as a whole, direct action on the autonomic nervous system, and changes in the endocrine glands (68, 120).

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