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# The Effects of x-rays and gamma rays on inflammations

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# THE EFFECTS OF X-RAYS AND GAMMA RAYS ON INFLAMMATIONS

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# OUTLINE


INTRODUCTION

I HISTORICAL SURVEY

II GENERAL EFFECTS ON INFLAMMATION

III SPECIFIC EFFECTS

IV PHYSICAL FACTORS INVOLVED IN RADIOTHERAPY

V RADIATION THERAPY IN SPECIFIC INFLAMMATIONS

VI CORRELATION OF X-RADIATION WITH OTHER THERAPY

TABLE OF CONTENTS


| | Page No. |
|---|---|
| INTRODUCTION | 1 |
| HISTORICAL SURVEY | 4 |
| PROPHYLAXIS | 13 |
| THERAPEUSIS IN ACUTE INFLAMMATIONS | 17 |
| " " CHRONIC " | 19 |
| PHYSICO-CHEMICAL EFFECT | 22 |
| EFFECT ON CELLS | 25 |
| PHYSIOLOGICAL EFFECTS ON CIRCULATION | 30 |
| " " " HEMOPOIETIC SYSTEM | 32 |
| " " " CONNECTIVE TISSUE | 35 |
| " " " INTEGUMENTARY STRUCTURES | 36 |
| " " " NERVE TISSUE | 37 |
| EFFECT ON PHAGOCYTOSIS AND ANTIBODIES | 39 |
| " " BACTERIA | 42 |
| " " PROTOZOA | 46 |
| " " FUNGI | 46 |
| X-RAY GENERATORS VERSUS RADIUM | 48 |
| TECHNICAL FACTORS | 48 |
| DOSAGE | 50 |
| FURUNCLES, CARBUNCLES AND OTHER PYOGENIC INFECTIONS | 52 |
| ACUTE PAROTITIS | 54 |
| ERYSIPELAS | 56 |
| MASTOIDITIS AND OTITIS MEDIA | 57 |

TABLE OF CONTENTS (Cont'd.)


| | Page No. |
|---|---|
| LYMPHADENITIS | 60 |
| GAS GANGRENE | 61 |
| MASTITIS | 63 |
| PNEUMONIA | 64 |
| LUNG ABSCESS | 66 |
| PERTUSSIS | 66 |
| SINUSITIS | 68 |
| CHRONIC SINUSITIS | 69 |
| ACTINOMYCOSIS | 70 |
| BLASTOMYCOSIS AND OTHER FUNGI INFECTIONS | 71 |
| PULMONARY TUBERCULOSIS | 72 |
| TUBERCULOUS ADENITIS | 73 |
| " PERITONITIS | 74 |
| " INFECTIONS OF THE EYE | 75 |
| UROGENITAL TUBERCULOSIS | 76 |
| BONE AND JOINT TUBERCULOSIS | 78 |
| UNRESOLVED PNEUMONIA | 78 |
| GONORRHEAL INFECTIONS | 79 |
| ARTHRITIS DEFORMANS | 80 |
| CHRONIC ARTHRITIS | 81 |
| OSTEOMYELITIS | 82 |
| EAR, NOSE AND THROAT INFECTIONS | 83 |
| OPHTHALMOLOGICAL INFECTIONS | 84 |

TABLE OF CONTENTS (Cont'd.)


| | Page No. |
|---|---|
| PEPTIC ULCER | 85 |
| BRONCHIECTASIS | 87 |
| CARDIAC CONDITIONS | 87 |
| NEURITIS AND NEURALGIA | 90 |
| ACNE VULGARIS | 93 |
| TUBERCULIDES | 94 |
| TINEA TONSURANS | 95 |
| FAVUS | 95 |
| FUNGI INFECTIONS OF THE SKIN | 95 |
| HERPES ZOSTER | 96 |
| ECZEMA | 96 |
| LICHEN PLANUS | 97 |
| SYCOSIS | 97 |
| MYCOSIS FUNGOIDES | 98 |
| PSORIASIS | 98 |
| DOSAGES USED IN ACUTE INFLAMMATIONS | 99 |
| " " " CHRONIC " | 100 |
| " " " DERMATOLOGICAL INFLAMMATIONS | 101 |
| CORRELATION OF RADIATION WITH HEAT | 102 |
| " " " " ULTRAVIOLET RAYS | 105 |
| " " " " SURFACE APPLICATIONS | 105 |
| " " " " SURGERY | 106 |
| " " " " SERA AND BACTERIAL THERAPY | 107 |

TABLE OF CONTENTS (Cont'd.)


| | Page No. |
|---|---|
| CORRELATION OF RADIATION WITH DRUGS OF SPECIFIC ACTION | 108 |
| CORRELATION OF RADIATION WITH PALLIATIVE DRUGS | 110 |
| BIBLIOGRAPHY | 111. |

# INTRODUCTION

In the mind of the average medical practitioner as well as the mind of the laity, the idea of radio-therapy has been linked with the treatment of malignancy. In this field, X-ray and radium have shown their effectiveness and have been quite generally accepted as being of definite value. However, many physicians do not realize the fact that great strides have also been made in the treatment of inflammations and that at the present time, its value has been proved by roentgenologists in both Europe and the United States. In some conditions, such as post operative parotitis, acne vulgaris, unresolved pneumonia, erysipelas, tinea tonsurans, mycosis fungoides and carbuncles, it is practically considered a specific.

There are several reasons for the slow acceptance of this form of therapy in inflammations. The one of greatest consequence is likely the fear of deleterious effects such as have followed cancer therapy in certain cases or following over-exposure to the rays. The therapy of malignancies requires the administration of the maximum dose that the surrounding normal tissues will tolerate and this margin of tolerance may be overstepped unless great skill and judgment is used. Therapy of inflammations, on the other hand, requires small, mod-

erate doses and if properly administered by a competent roentgenologist, the danger is practically nil. To further illustrate the point, the following observation may be mentioned. It has been noticed in the literature that often the first indication that radiation may be of value in a given inflammatory condition has come as an unexpected clinical improvement after the brief exposure to X-rays required for radiographic diagnosis or "check-up." Such was the case in the treatment of mastoiditis for example. (1)

Two other factors are: The over-enthusiastic radiologists who have exaggerated the possibilities and have at times brought radio-therapy into disrepute by practicing a type of "quackery;" and the uninformed members of the medical profession who have discountenanced its use, in the face of abundant evidence as to its definite value in inflammatory conditions.

With these points in mind, I have attempted to review some of the literature with particular reference to the proper use of X-radiation indications, contra-indications and correlated treatment in specific inflammations. Such a review may be of value because the present status of radiation therapy is largely on a basis of

clinical results, even though much has been learned as to some of the mechanisms involved.

# I HISTORICAL SURVEY

William Konrad Rontgen on the eighth of November, 1895, while working alone in his laboratory with a Crooke's tube, noticed the fluorescence of a distant card coated with platino-barium-cyanide. He found that the rays which supposedly were the cause of the fluorescence could penetrate cardboard, wood or paper and proceeded to discover their properties which set them apart as a form of radiation which had never been described before.

X-rays had previously been produced by William Crookes seventeen years before. However, he failed to recognize them. Hertz, Lenard and others also produced the rays in their experiments but did not recognize the unusual force at their finger-tips.

In Rontgen's original announcement (2) he very completely described the rays and many of their properties which he had determined. He insisted on checking all his observations as far as possible by means of photographic plates.

It is remarkable how quickly the news of one of the most beneficient miracles of science was accepted although peculiarly opposed to universal experience. Skepticism was silenced by confirmation from reliable sources on every hand. Since that time, extensive experimentation has been carried out by scientists in

all parts of the world attempting to determine the effect of the rays on both normal and pathological tissues as well as upon micro-organisms. Within a few months after Rontgen's announcement, their possible therapeutic value was being tested both in the United States and in Europe. Much of the advance made in X-ray therapeutics has been by trial and error methods with the consequent trail of success and failure and also the development of erroneous ideas which later had to be discarded.

It was difficult to correlate the results obtained in different cases because of the variability of X-ray apparatus in use and the lack of a suitable standard of dosage. This inability to reduplicate the treatment as given by another investigator, held back the progress of evolution of this new weapon against malignancy and disease. Many different dosimeters were designed with various degrees of success.

The "erythema dose" was one of the common methods of measuring the radiation given but there has been very little agreement among roentgenologists as to the factors of this biological unit. Patients do not react alike to radiation and various parts of the same individual give a different reaction to the same intensity of radiation. In spite of these disadvantages, the erythema dose has continued to be used.

Then in 1914, the Coolidge thermionic tube was developed, which made possible a constant source of radiation. It made available large quantities of radiation which could be duplicated by other operators and well controlled. With this new development, it has become practicable to standardize the "erythema dose" or give the amount of radiation intensity it represents in terms of definite factors. This is done by means of a standard secondary ionization chamber and the dose is then determined in terms of "roentgens." The roentgen was defined in 1928 by the International Roentgen Ray Committee as "the quantity of roentgen radiation which, when the secondary electrons are fully utilized and the wall effect of the chamber is avoided, produces in one cubic centimeter of atmospheric air at zero degrees Centigrade and 76 centimeters of mercury pressure, such a degree of conductivity that one electrostatic unit of charge is measured at saturation current." (3)

Soon after Rontgen's discovery in 1895, several physicists began to experiment with various substances to determine whether similar rays might be emitted by chemical bodies spontaneously. Henry Becquerel experimented with various substances which fluoresced and found that salts of uranium produced a penetrating radiation. He then postulated a new property of matter--radio-activity. (4)

Pierre Curie and Mme. Curie studied the activity of the uranium compounds and found that it depended entirely on the amount of uranium present. This led to the conclusion that radio-activity was an atomic phenomenon and not influenced by chemical combination or external conditions. Finding some uranium ores which were more radio-active than either pure thorium or uranium, the Curies were inspired by the thought of a new element. In July, 1898, polonium was identified and also radium. This was announced before the Academy of Science of Paris in December, 1898.

In 1902, Rutherford and Soddy worked out the theory of successive transformations of radio-active elements. Mme. Curie devised a method for determining the quantity of radium present in a substance by means of a radio-active gas produced by its disintegration. This was called "emanation."

The first experiments to determine the biologic properties of radium were made in France from samples obtained from the Curie laboratory. These were so encouraging that a new phase of medicine became established.(5)

X-rays, gamma rays and Grenz rays are all a part of the electromagnetic wave spectrum of which light, ultra-violet, infra-red, radio or Hertzian waves and cosmic waves are also members. There has been some controversy as to the

difference in biological effect of the three radiations first named.

Holthusen (6) in 1933 came to the conclusion that radium radiations or gamma rays do not act any differently than roentgen radiations. However, in one series of experiments, he finds that when X-rays of equal intensity to a given radium pack, as measured in roentgen units to the area, are applied, the erythema reaction produced by the radium is about 20% stronger than that of the X-ray. According to clinical observations made by Kaplan (7) the biological effect of radium is the greater. However, many others do not agree with him on this point. Nevertheless, it is more or less generally agreed by most authorities that both radium and roentgen rays bring about their biological action by means of ionization and that there are only minor differences, if any, in the results obtained. (3)

Filtration of these radiations has a definite effect on the quality of rays allowed to pass through and affect the region treated. Aluminum, ~~for example, filters off the hard rays or shorter wavelengths while~~ and copper filters off the soft rays or longer wavelengths. Thus, the X-radiation may be varied to considerable extent and made to simulate gamma radiations of radium. (3)

Surprising as it may seem, the use of X-rays and gamma

rays in treatment of inflammations has been carried on almost from the time of their discovery. Within a few months after Rontgen's announcement, their therapeutic value was being tested.

TUBERCULOSIS: Experiments of Lortet and Genoud in 1896 (Tuberculose experimentale attenuee par le radiation Rontgen, Arch. d'electr. med. 4:466-467) showed a favorable influence of the rays on tuberculous adenitis. Also the clinical reports of Rendue and Du Castel (Sur un cas d'application des rayons rontgen au traitement des phlegmasies aigus de l'appareil thoracique, Bull. et mem. Soc. med. d. hop de Paris 14:41-55, 1897) and others indicate that in certain cases roentgen rays have a definitely beneficial effect on the tuberculous process. (8)

NERVE INFLAMMATIONS: In 1897, Gocht H. (Therapeutische Verwendung der Rontgenstrahlen Fortschr. a.d. Geb. d. Rontgenstrahlen I 14-22, 1897-1898) reported analgesic effect in three cases of trigeminal neuralgia and two of mammary cancer. Since then a large number of cases have been reported in which roentgen rays have abolished neuralgic pains and pruritis in many different conditions. (9) Paravertebral irradiation was first used in the treatment of angina pectoris in 1923 and was reported by Groedel (Rontgenbehandlung innerer Krankheiten, J. F. Lehmann p. 209, 1923). Over 100 cases have been

reported in the literature with favorable results. (10)

BRONCHO-PNEUMONIA: Rendue and Du Castel in 1897 (Bulletin Medicale Jan. 17, 1897) reported the use of X-rays in a case of bronchopneumonia with apparently favorable results. (11)

ARTHRITIS: The first report of the use of roentgen therapy in the treatment of arthritis was that of Sokolow (Roentgen Rays, Russky Vratch, 1897) also (Fortschr. a.d. Geb. d. Rontgenstrahlen 1:209, 1898) who used it for relief of pain in articular rheumatism. (12) (13)

DERMATOLOGICAL CONDITIONS: As early as 1896, Ullman (System of Instruction, Monell, 1902) reported a cure of acne treated by X-rays. In 1898, Gautier (System of Instruction, Monell, 1902) treated three cases with good results. (14) (15) Since that time, many cases have been treated and hundreds of cases reported with such outstandingly good results that Tobias (16) makes the statement that there are only two agents that will cure acne--nature and the roentgen ray. Since nature allows unnecessary scarring, the roentgen ray is the best method to secure permanent cure with the minimum amount of scar formation.

Freund is also among the first to apply the rays to dermatological conditions. Their use in tinea tonsurans (ringworm of the scalp), favus and sycosis was suggested

by him in 1897 (Wien, med. Wochens XLVII p. 856, 1897). Some successfully treated cases were reported as early as 1889 by Freund and Schiff (Fortschr. a.d. Geb. d. Rontgenstrahlen iii p. 109, 1899). Kummell, at the 22nd Congress of the Deutsche Gesellschaft fur Chirurgie. April 22, 1897, gave a report on the treatment of lupus and Gocht (Fortschr. an. dem Gebiete der Rontgenstrahlen, Sept. 1897) reported six cases of lupus. (11)

Dr. R. Hahn claims priority in radiotherapy of eczema. In 1898, he reported two cases successfully treated, at a meeting of the Medical Society of Hamburg (Fortschr. a.d. Geb. d. Rontgenstr. 1901 pp. 39-41). (17)

TRACHOMA: As far back as 1902 Mayou recorded sixteen cases of trachoma which were treated with X-ray. Using one eye for a control with the usual copper sulfate treatment, the other irradiated eye healed in much less time and gave a complete cure in five cases while nine were favorably improved and the remaining one was still under treatment. (18) (19)

ACTINOMYCOSIS: Harsha successfully treated a case of actinomycosis with X-ray, drainage and iodides in 1904. (20) Many cases have been reported since that time which were treated only with X-ray and possibly surgery. (21)

PNEUMONIA--Delayed Resolution: In 1905, Musser and Edsall (22) suggested the use of X-ray in cases of unre-

solved pneumonia on the basis that it would probably aid the autolytic process. With this idea in mind, they treated one case of unresolved pneumonia with rapid improvement at the end of a week. A. J. and W. A. Quimby (23) report twelve such cases and make the statement that "no pathological process in the body responds more quickly to X-ray exposure than non-resolution following pneumonia." Other cases have been reported by Krost in 1925 (24), Torrey in 1927 (25) and Merritt and McPeak in 1930. (26)

NEPHRITIS: Pescarolo and Quadrone (Risultati favorevoli della roentgenterapia nella nefrite parenchimatosa cronica. Rif. med. 23: 1021-1023 Sept. 15, 1907) treated a woman with nephritis. The symptoms included edema, ascites and hydrothorax. Upon treatment, the condition of the patient began to improve immediately and a complete recovery followed. Several cases with oliguria or anuria and other symptoms of renal insufficiency have been reported, in which rapid and marked improvement followed irradiation of the kidneys. (27) (18)

PELVIC INFLAMMATORY DISEASE: Wagner (Die Rontgentherapie der entzundlichen Erkrankungen in der Gynakologie. Strahlentherapie 24: 52-72, 1926) reports 350 cases of acute, subacute and chronic inflammations of the female genital structures with exceptionally favorable results with the puerperal form of parametritis and also gonorrheal

infection. (27)

SUPERFICIAL PYOGENIC INFECTIONS: Morton in 1903 tried radiation on an extensive carbuncle of the neck with marked success and rapid recovery. (13) The literature contains many reports of success of radiation in the condition as well as furunculosis and onychitis, etc.

PAROTITIS: The first record of the influence of X-rays in the treatment of acute parotitis seems to have been made by Heidenhain in 1926 (Rontgenbestrahlung und Entzundung. Strahlen-therapie 24: 37-51, 1926). (28)

To Heidenhain and Fried belong the credit of having created a more general interest in the radiation therapy of inflammation. In more than 1500 cases they have proved the effectiveness and have helped to place the matter of dosage on a scientific basis. (13)

## II GENERAL EFFECTS ON INFLAMMATION

### A. PROPHYLAXIS

There has been some controversy as to any possible prophylactic action of X-rays. Much of the work done in this direction has been along the line of noticing the effect of irradiation on the healing time of wounds, with and without the subsequent introduction of infection.

Haberland in 1923 (Klin Wchnschr. 2:353, 1923) irradiated Thierschgrafts in dogs and found delayed healing. The dose used was probably 1/3 to 2/3 of a skin unit dose. Podesta (Riv. di. radiol. e. fis. med. 2:446, 1930) used a simple epilation dose causing a severe radio-dermatitis and noticed delay of healing ranging to complete lack of closure. (29) Pohle, Ritchie and Wright in 1931 found that if the exposure of the wounds was made 24 hours after incision there was definite retardation of healing but it did not interfere with the final formation of a smooth scar. However, they used 1000 r. in one sitting which is well above the therapeutic range. (30) In 1933, Pohle and Ritchie (31) on experiments with 78 rats, in which half of each wound was irradiated and the other half protected, found by means of daily microscopic sections, that there was delay in healing in wounds treated after 24 hours and this became evident 3 to 4 days after the wound was made.

On the other hand, Cazzamali (Abst. Clin. chir. 4:781, 1928) injected trypan blue into tissues a few days before and immediately following wound production. He concluded that radiation caused an earlier mobilization of reticulo-endothelial elements in the healing process. Freudid (Strahlentherapie 33:375, 1929) and Fukase (Virchows Arch. F. path. anat. 273:794, 1929) found that 400 r. applied to freshly made wounds, accelerated the healing with a decrease in inflammatory exudate, particularly leucocytes. Businco and Cardia (Riv. d. radiol. e. fis. med. 2:378, 1930) using 1/3 erythema dose (about 150 r.) on dogs, concludes that there is a stimulation and acceleration of healing. D'Istria and di Bello (Actinoterapia 9:95, 1930) reported an acceleration of healing by using doses ranging from 63 to 1000 r. They conclude that the smaller the dose the greater the acceleration within this dosage range. (29) Leopold Freund in 1898, noticed the beneficial influence of X-rays on keloids and bad scars. Since then he has gotten very good results by the irradiation of the open wound for several days after the removal of a tumor and before the wound was covered with skin. Clinically, he has observed many times the acceleration of healing of wounds after exposure to X-rays. (32) Then Franz. Freund in 1929 reports a series of experiments on rabbits. He incised the skin of the abdomen and irradiated part of

the wound. This part healed by first intention and with granulation. The edges closed on the 5th day while on the non-irradiated side the wound was still gaping. He also showed that fractures heal more quickly and wounds on the cornea of frogs' eyes heal more readily after irradiation. He concludes that the use of irradiation prophylactically is justified. (33) These results have been confirmed by Tannenberg and Bayer in 1933. (34) They carried out similar experiments and found that the irradiated wounds began to heal 3 to 20 hours earlier. The healing was also more quickly accomplished.

Ritchie draws the following conclusion from a survey of the literature. "Thus in spite of somewhat conflicting evidence, it appears that a small dose stimulates the healing process and a large one causes delay." (29)

In regard to the introduction of infection on prophylactically treated animals, Quadrone in 1905 ( Centralbl. f. inn. Med. 26:593, 1905) concluded that mice and guinea pigs which had been exposed to X-ray showed greater resistance to infection than did normal animals. Heile (Verhandl. d. Deut. Gesell. f. chir. 34th Congress, 1905) produced a local leucocytosis in the peritoneal cavities of rabbits by injecting aleuronat and then injected B. Coli. The animals were divided into two groups and one exposed to X-ray. The other group died of the infection

while the irradiated group survived. Werner (Munch. Med. Wochenschr. 53:1625, 1906) produced turpentine abscesses and later injected them with bacteria. One-half of the animals were irradiated and recovered. The rest died from progressive inflammation. Heile and Werner explained their results on the theory that the X-rays destroyed the leucocytes in the peritoneal cavity setting free substances which were bacteriocidal in action upon the organisms present. (35)

In the case of tuberculosis there has been much experimentation tending to prove that resistance of most animals is lowered. This is explained on the basis of lymphocytic destruction. The lymphocytes being thought to represent the natural resistance of the organism to the tubercle bacilli. Murphy and Ellis have reported such experiments (36) as well as Morton in 1916 (37) and Corper in 1918. (38) Spies (39) found a diminution in the number of lymphocytes and a relative increase in polymorphonuclear leucocytes after irradiation.

Kellert in 1918 (40) failed to confirm Morton's work and Kessel and Sittenfield (41) found that irradiated tuberculous animals lived on an average of 15 days longer than those not exposed. The conflicting reports may be due to differences in irradiation technic. The early investigators undoubtedly used lower dosage due to the

limitations of their apparatus, so perhaps a lymphocytosis was produced with consequent increase in resistance to T.B. (40)

More recently Kissele (42) (in 1936) after experiments on 54 guinea-pigs and 500 white mice comes to the following conclusions:

1. X-rays in doses of 100 K.v., 4 ma., 3 mm. Aluminum increase both local and general resistance to infection.

2. The local increase of tissue resistance after doses of 1, 3/4 and 1/4 skin erythema continues 3 to 4 weeks and gradually declined to normal.

3. General resistance is favored when considerable portions of the body are irradiated.

4. Smaller doses have little, if any, effect on resistance.

In regard to gas gangrene, Kelly and Dowell (43) come to the following conclusion after treating a series of 56 cases: X-ray therapy is indicated in gas gangrene and should be started as soon as the disease is suspected.

B. THERAPEUSIS

1. ACUTE INFLAMMATIONS

In general the action of X-rays applied in therapeutic doses to superficial inflammations is: (a) Possible exaggeration of symptoms during the first 12 hours, (b) Relief of pain within the first 24 hours, a drop in temperature and improvement of appetite, (c) If the process

is treated early with irradiation, it may be aborted, i.e., abscess formation may be prevented expediting involution and without scar formation, (d) If irradiated late after abscess formation has begun, the suppuration will be hastened and free drainage may occur spontaneously. The course of the condition is materially shortened.

The above description may be found through out the literature--Lewis, 1923 (44), Hodges, 1924 (45), 1925 (46), Lawson, 1926 (47), Andrews, 1929 (48), May, 1930 (13). Friedman, 1934 (49) reports the following general results after the treatment of 206 cases of carbuncles. Pain was relieved in 24 hours. The temperature dropped in 36 hours. There was spontaneous healing if no liquefaction was present at the time of treatment. If suppuration occurred before treatment a stab incision was made and the course was considerably shortened.

Hodges (50) reports Mittermaier as summarizing the action of the rays thus: (1) Early--an increase in edema but a tendency to check abscess formation. (2) Later--after reparative processes have begun, these processes are accelerated. (3) Inflammation ceases to spread. Disintegration of tissue in the process of destruction occurs more rapidly and time of recovery is shortened.

Gerber (51) adds one more point in the effect on the healing process after suppuration and drainage have

occurred. Granulation tissue is promoted and a better scar is produced. Lewis (44) describes the scar as "smooth, soft, not depressed and distinguishable from other tissues by its pallid color."

In 1932, Thorsness (52) after experimenting with absorption thru the pyogenic membrane of irradiated experimental abscesses, concludes:

(a) Non-irradiated abscesses show no absorption for months.

(b) Abscesses, if irradiated 1 or 2 days after formation will collapse after 6 days.

(c) If irradiated after 7 days, there is little or no effect. He used dosages probably equivalent to 1/4 to 1/2 erythema dose for human beings.

2. CHRONIC INFLAMMATIONS

The chief effect of X-radiation upon chronic inflammatory processes is one of resolution of the fibrotic process. The most outstanding example of this occurs in the treatment of unresolved pneumonia. In 1907, Edsall and Pemberton (53) reported five cases in which consolidation had been present for at least 7 to 10 days and radiation gave good results. In 1916, Quimby, A.J. and Quimby, W.A. (23) come to the conclusion that "no pathological process in the body responds quicker to an X-ray exposure." Krost in 1925 (24) reports 12 cases with which he conclusively demonstrates the resolving effect of ir-

radiation. He took radio graphs to prove the presence of consolidation before and the absence of consolidation after treatment. Torrey (25) describes a case which had a patch of unresolved consolidation from a pneumonia of 5 years previous. This responded immediately to treatment. Merritt and McPeak, 1930 (26) report that parenchymal resolution occurs rapidly while hilar lesions are slower to respond.

In tuberculosis, particularly cervical adenitis the effect is usually quite definite. Leonard as early as 1910 (54) reports three cases irradiated with good results. Kessel and Sittenfield in 1914 (41) tried Xprays on experimental T.B. and found fewer fibrosed tubercles with a less amount of caseation. Reeves (1933) (55) after treating 141 cases of tuberculous cervical lymph nodes states that small doses used at intervals of less than 3 weeks appear to shorten the course and favor resolution.

Arthritis has been treated on the basis of analgesia and also resolution of fibrotic processes. Anders, Daland and Pfahter in 1906 (56) reported good results in 2 cases of Arthritis deformans. After 16 treatments, the joints were practically well. Garland in 1935 (12) treated 30 cases of Gonorrheal arthritis and reports 13 cures, 15 improved and 2 not improved. Rohr, H. O. (Die Rontgenther. der chr. arthritiden. Strahlentherapie 42:425, 1931) reported 40 cases of chronic arthritis with good results.(12)

Carl Fried (57) reports results on 135 cases of arthritis deformans, the greater number of which required only one irradiation series for marked improvement. Arthritis in the hip joint showed the largest percentage of failures. He states that chronic articular rheumatism even with stiffening and contractures can be improved and even cured.

## III SPECIFIC EFFECTS

### A. PHYSICO-CHEMICAL EFFECT

Ionization is the only thing to which all the effects of irradiation may be attributed. The sequence of events may be assumed to be: (a) Ionization of the tissues, followed by (b) Chemical changes and then (c) Biological changes. There may then be further chemical changes as a result of the first biological changes, etc. This view accounts for the latent period in the appearance of the effects of irradiation in the living organism.

In general, the tendency in this process of chemical recombination, after ionization has occurred, is to transform complex molecules into simpler compounds. For example, water may be decomposed into hydrogen and oxygen but at the same time some hydrogen peroxide is formed. (58)

Doub, Bolliger and Hartman in 1925 (59) found that during the first hour following irradiation there is an increase in phosphorus and a decrease in amino acids and non-protein nitrogen within the nuclei of the cells. They also described the production of a distinct alkalosis of the blood on the theory that it was brought about by nuclear destruction which yeilded purine bases. Then, if the dosage had been moderate, there was a compensatory acidosis within 24 hours. They also found a rise in blood sugar, with a fall and a secondary rise on the third day following the

irradiation. This was probably due to the hexoses formed from the destroyed amino acids and the deaminization of amino acids by increased enzymic action.

Many divergent opinions are held regarding the change in hydrogen ion concentration of protoplasm after irradiation. It is reasonable to expect, however, that if the radiation is intense enough, the cells are severely injured the $P_H$ will turn to the acid side due to the decomposition products. (60)

Beta, gamma rays and X-rays when applied to positively charged lyophobe suspensoids cause a precipitation while positively charged lyophile suspensoids set to a gel. Emulsoids such as proteins are denatured by X-rays or gamma rays whether positively or negatively charged, but only after prolonged radiation. This denaturization is accompanied by an increase in viscosity and a decrease in surface tension and is more marked in globulins. (61)

In regard to intracellular proteins, most investigators are agreed that irradiation causes first a decrease in viscosity or coagulation (61) the cell metabolism reduced or brought to a standstill. (62)

One of the most obvious and clearly attested physical phenomena resulting from irradiation is the increased permeability of cell membranes and probably also of the nuclear membrane. The swelling of the nuclei and the

ballooning of the cytoplasm are most easily interpreted as an increased capacity of the structures to absorb water thru an altered membrane. Assuming the simplest cause, one must suppose that intracellular chemical changes produce new electrolytes by decomposition of salts, proteins and fats and water is drawn in by simple osmosis. (62)

There is reason for believing that the plasma membrane of the cell is in part at least, a calcium gel. Release of calcium would presumably liquefy or weaken such a gel. Hence, it is understandable that radiation should break down the cell membrane. Moreover, in view of the fact that calcium, more than any other ion, is responsible for the semipermeability of the membrane, it is readily conceivable that release of calcium from the cortex of the cell or from the membrane might cause the permeability increase as noted above. These facts are in accord with the observations which show that calcium is set free from plant and animal tissues after irradiation. A similar effect has been described for proteins and it may be interpreted in terms of a known action of rays on the carboxyl bond of amino acids. (63)

"The coagulation produced by radiation is evidenced morphologically by the appearance of vacuoles within the cell. Experimental evidence is in favor of the view that the calcium released from the membrane differs to the in-

terior of the cell and causes the ultimate coagulation of the main mass of protoplasm." (63)

B. EFFECT ON CELLS

Ewing, 1926 (62) describes the primary effect of radiation as an enormous swelling of the cell with hyperchromatism of the nuclei especially after large doses. He suggests that the mechanism consists of an inbibition of water by the nucleoproteins, probably at the expense of the cytoplasm which is not simultaneously increased. This has also been described in section III A. in regard to the change in permeability.

Packard, 1931 (60) regards the cellular changes after radiation as the same as those accompanying degeneration by other means. "When the short radiations are absorbed by the cell they quickly change the rythm of mitosis. The cells which are about to divide are prevented from beginning that process. Unless the radiation is very intense or long continued they suffer no visible injury and begin to divide soon after the exposure stops. This temporary check in the onset of mitosis is followed by a considerable increase in the number of dividing cells, the result being that the total number of divisions occurring within the space of a few hours after exposure is about normal. This is due to the fact that cells already in mitosis when irradiation begins, complete the division which they

have started.

Clark (64) from his survey of the effects of X-radiation gives the following primary effects: (a) Increase in $P_H$ (b) Increase in cell membrane permeability (c) Increase in viscosity of the protoplasm. The secondary effects which come as a result of the primary are: (a) Inhibition in subsequent growth and development (b) Shrinking and clumping of chromosomes (c) Rate of cell division is depressed.

There appears to be a correlation between the rate of division after exposure and the ability to recover. Cell reparative processes after radiation go on more readily when all division is checked. (60)

It should be mentioned also that heavy radiation may affect the distribution of the chromosomes within the nuclei of the cells and thus change the inheritance values. This effect is probably upon the chromosomes themselves or upon the surrounding protoplasm. Much of the work along this line has been done on the Drosophila or fruit fly. (65) Reviews of this effect are described by Packard (60), Clark (64) Dobzhansky (66) and Schultz. (67)

According to Doub (59) effects of radiation may be counteracted by substances which protect the cell; for example--ether anesthesia, morphine, glucose and calcium lactate.

"Radio-sensitivity seems to be an inherent quality of

the cell and may vary even in individuals of the same species." (68) This naturally is dependent upon many factors in the constitution of the cell such as: (a) The presence of certain proteins, inorganic ions and enzymes (b) The permeability of the membrane and (c) The relation to its source of nutrition. In general, however, rapidly growing tissues are highly susceptible. So also are cells in which differentiation is not great. The same amount of energy is absorbed by all kinds of cells but the different quantitative effects may be due to the chemical make-up of the cells or to the relative stability of the compounds or to the difference in regenerative power. The experimental proof for this idea is not abundant because of the difficulty of carrying out investigations along these lines. (60) The order of cell sensitivity to radiation is generally accepted to be as follows:

1. Lymphoid cells
2. Polymorphonuclear and eosinophilic leucocytes
3. Epithelial cells
    (a) Basal epithelium of certain secretory glands--for example, salivary glands
    (b) Basal epithelium of testes and follicular epithelium of ovary
    (c) Basal epithelium of the skin, mucus membranes of stomach and small intestine
    (d) Alveolar epithelium of lungs, epithelium of bile duct

(e) Epithelium of kidney tubules

4. Endothelial cells of blood vessels, pleura and peritoneum
5. Connective tissue cells
6. Muscle cells
7. Bone cells
8. Nerve cells (64)

The most resistant cells are listed by Warren (69) as:

1. Adult thyroid
2. Adult pituitary
3. Brain and nerve cells
4. Nerve trunks and nerve endings
5. Tendon and joint capsules
6. Adult sperm cells
7. Red blood cells

The red blood cells are the most resistant.

In regard to stimulation of cell activity as a possible effect, Packard (60) makes a very clear summary of the present status of this idea. "The term is unfortunate because in its proper sense, it means any change in the state of the organism, whether excitation or depression. Its use in radiological literature has been to refer to a reaction favorable to the organism as an increase in growth or an increase in functional activity. Many experiments show that weak radiations may accelerate the rate of mitosis

and of growth in animal cells. In most cases, this reaction is short lived or terminates in an obvious injury. The evidence now at hand points to the conclusion that radiations do not directly stimulate the normal activities of the cell. Their primary effect is always an injury from which the cell may recover perfectly. But the degeneration products which arise after irradiation may temporarily quicken the tempo of some normal processes such as mitosis and protoplasmic streaming. Such reaction is secondary and is not true stimulation in the sense of the word used in radiological literature."

In contrast to this view, Isaacs (70) (71) has been promulgating the idea of stimulation of cells as being the primary effect of radiation. He has studied a large number of cases (some 1800) from the standpoint of blood findings before and after radiation. He concludes that stimulation is the primary action and that the results depend upon the stage of development of the cells at the time of radiation. "Cells in the myoblastic, lymphoblastic or younger stage are stimulated to rapid reproduction. Whereas cells in the myelocytic stage or medium-sized lymphocytic stage are stimulated to grow thru the rest of their life history because normally they do not divide or multiply."

C. PHYSIOLOGICAL EFFECTS ON DIFFERENT TISSUES AND TISSUE FUNCTIONS

For a long time, it was thought that radium rays were

more effective therapeutically than X-rays, that the tissue reaction was less deleterious, etc. There was a great deal of clinical evidence to support this. However, more recent work has shown conclusively that the favorable clinical effects following the use of radium are not due to any specific action but rather to the fact that the intensity of the beam is low. When X-rays are delivered at comparable intensities, the tissue reactions are the same. When a beam of high intensity is absorbed, the very extensive ionization which follows brings about destructive changes in all of the cells whether they are naturally resistant or sensitive. None escape injury. The slight damage done by a beam of low intensity is repaired by the resistant cells as rapidly as it is inflicted so even after a period of long exposure they appear unharmed. (72)

1. CIRCULATION

Maximow (73) in his study of the histological changes of inflamed tissue after irradiation describes the blood vessels as showing swollen endothelial cells and some fragmentation of the nuclei. This was with a dose large enough to develop alopecia in most of the experimental animals and superficial inflammation in some. Similar descriptions were made as early as 1904. (11) Warren in 1928 (74) summarizes the effect on capillaries

as follows:

1. Engorgement - which is greatest with high intensity of dose
2. Hypersensitiveness to adrenalin (after irradiation)
3. Distinct lessening of constricting and dilating powers (after erythema dose)
4. Permeability is at first increased and then decreased
5. Connective tissue injury and endothelial injury--obliteration

Seelig (68) in his experiments on vascularity and its relation to radiation finds that areas of compromised blood supply reacted in much the same way to irradiation as did normal tissue with the exception that there was hyperplasia of the epithelium resulting in the presence of many young active cells. However, the radio-sensitivity of the cells did not appear to increase appreciably in comparison with unaltered epithelial cells in the same animal.

Pullinger (75) is of the opinion that most of the effects of irradiation are on the basis of circulatory disturbance. He states that "hyperemia is the essential reaction to therapeutic irradiation" the thin-walled, loosely supported capillaries being most readily affected. Then if the dose is severe, endothelial injury follows excessive distention and the hyperemia is succeeded by exudation of serum, extravasation of blood and finally intra-

vascular thrombosis. He therefore sums up all the effects of radiation as related to vascular stimulation and vascular degeneration.

2. HEMOPOIETIC SYSTEM AND BLOOD

It has been known for a long time that the spleen and lymph nodes contain large numbers of lymphocytes that are sensitive to radiation. (76) (22) (77) Heineke (Wchnschr. 51:785, 1904) by means of experiments on small animals demonstrated that lymphoid tissue was primarily affected. There was degeneration of the lymphoid follicles in the spleen and lymph glands and diminution in the number of circulating lymphocytes. (76) Warthin (77) describes the effects on the spleen as being "disintegration and destruction of lymphoid elements of splenic pulp and follicles, as well as degeneration of phagocytes, giant cells and epithelioid cells of the follicles." The lymph glands show:

1. Destruction of lymphoid cells
2. Small lymphocytes are killed before any other cells
3. Slight irradiation causes fatty degeneration and vacuolization
4. Intense irradiation causes nuclear disintegration

The bone marrow, in general, shows less effect of the radiation but after long radiation there is destruction of the myelocytic types of cells. Undoubtedly, there is inhibition of the white cell production after irradiation

as there is a preponderance of senile forms over the younger.

There is much literature bearing upon the subject of the sensitivity of the lymphocytes and lymphoid tissue to irradiation. Most of the experimental results obtained agree essentially with those found by Warthin (77) Heineke, etc. Akaiwa and Takeshima (78) describe the reaction of lymphoid tissue as occurring in three periods:

(a) First 12 hours - increase in size of node, nuclear disintegration and decomposition of the germinal center

1. If a small dose, there may be a great number of cells in mitosis

(b) 12 hours to 5 days - phagocytosis - clearing of cellular debris

(c) After 5th day - fibrosis of the node

Clark (64) sums it up in much the same way but adds that regeneration may begin within 24 hours if the dose has not been lethal. In regard to the bone marrow, he mentions the pyknosis of nuclei of the white blood cells and the fact that if the dose is large enough, only the red blood cells will be left.

In regard to the effect on various types of blood cells, there has been some disagreement. Nakahara (79) (80) (81) found a lymphocytosis experimentally with increased mitotic figures in the lymphocytes. He states that small doses of X-ray have no appreciable destructive effect on lymphoid tissues, but there is a "stimulation" which is

most pronounced about 2 days after in lymph nodes and 4 days after in the spleen. Taylor, Witherbee and Murphy (82) agree that the lymphocytes are affected first but find a sharp fall in the total number of circulating lymphocytes which is complete within 48 hours after irradiation and then followed by a primary rise which is followed by another fall, which in turn is followed by a permanent rise to normal. Russ, Chambers and Scott (83) are also of the opinion that the lymphocytosis always follows a primary lymphopenia. Other articles confirm this idea. (84) (85) (86) In 1921, Leitch (87) attempted to show that the lymphocytosis was in reality a fright reaction. This idea has received no credence in the later literature (76) (64) (70) (71) but the findings of a lymphocytosis with mild doses and a lymphopenia after larger doses is pretty well established.

Tsuzuki (88) gives the following order of sensitivity of the blood cells:

1. Lymphocytes
2. Monocytes
3. Eosinophils
4. Mast cells
5. Neutrophils

Kornblum, Boerner and Henderson in 1938 (89) make the statement that following therapeutic radiation, the

lymphocytes show a definite decrease in the majority of cases; the neutrophils show a slight depression; the monocytes and eosinophils apparently decrease but are not constant and the erythrocytes are not affected significantly.

3. CONNECTIVE TISSUE

Maximow (73) noticed in his histological study of irradiated inflamed tissue that the fibroblasts were most conspicuous and constant in their changes. That the nuclei were most affected and lost their capacity for normal mitoses. He suggests that the reason lies in the fact that the fibroblasts were the only cells preparing for mitotic division just following the introduction of the foreign body. (The experimental inflammation was produced by the introduction of celloidin blocks into intermuscular connective tissue.) He also states "the collagen fibrils are decreased in number and are coarser." Ewing (62) describes swelling and mentions degeneration of collagen fibrils and Warren (74) mentions the fact that actively growing fibroblasts are relatively sensitive to radiation. Clark (64) definitely states that connective tissue may be resolved. He also explains the increase in connective tissue cells in certain tissues and organs after repeated irradiation. "This is due to connective tissue being laid down to replace other cells which the rays have caused to undergo degeneration. It can be thought of as a secondary and indirect stimula-

tion as a result of a primary degeneration."

4. HAIR FOLLICLES, SEBACEOUS AND SUDORIFEROUS GLANDS

It has been known for years that these structures are affected by X-radiation. Oudin, Barthelemy and Darier (Monatshefte f. prakt. Derm. 25:417, 1897) made a careful study of the skin taken from areas of alopecia produced experimentally in guinea-pigs by X-ray exposure. They found that the bulbar end of the hairs was atrophic and thin and contained no pigment. The skin showed a thickened epidermis in all its layers and there were places where hair follicles had entirely disappeared. "The sebaceous follicles are merely downward projections of epidermis. There is no suggestion of a hair papilla or of any beginning regeneration." The radiation seems to increase the vitality of the least differentiated tissues while it produces degeneration and atrophy of the more highly differentiated structures. (11)

"Histological studies indicate that there is some atrophy of the sweat glands as a result of X-ray exposures." So Pusey (11) suggested the use of X-rays in hyperidrosis in 1901. He also mentions that "decrease in oiliness of the skin and in the size of the sebaceous follicles which is seen in acne under X-ray exposures is a matter of common observation."

Warren, in 1928 (74) states that "hair follicles,

sebaceous and sweat glands are probably as sensitive as basal cells (of the skin) but a slight disturbance in their function has more direct consequences."

Pohle (90) in describing skin reactions describes a first degree reaction as an epilation followed by tanning without visible inflammation and complete recovery. Therefore, a small dose may produce temporary epilation. A second degree reaction due to increased dosage will consist of moderate erythema and definite hyperemia, temporary epilation and pigmentation lasting about 6 to 12 weeks. A third degree consists of erythema with vesiculation, permanent epilation, loss of papillae and of sweat and sebaceous glands, lasting 8 to 15 weeks and heals with a thin scar which often developes telangiectasis. The fourth degree of course, is ulcer formation. The cumulative effect of numerous small doses may produce disappearance of hair papillae, sweat and sebaceous glands also.

5. NERVE TISSUE

Analgesic effects have been noted ever since 1896 but the exact basis is still in doubt. There is some evidence for believing that relief from pain is explainable in some cases on the release of pressure by the degeneration of surrounding cells but other factors must also participate because there is often an immediate effect which

cannot be explained on that basis because of the time element involved. (9)

According to most investigators, nerve tissue is very resistant to irradiation. (64) But it has been found that intense beta radiations from radium may destroy the functional capacity of a nerve trunk. There is a marked latent period between the irradiation and this loss of function, however. With increased intensity of radiation, the latent period decreases. There may be a slight increase in excitability followed by a decrease. The disturbance may involve both conduction and excitability. Histologically, little change can be noticed except for some fatty degeneration of the myelin sheath. (91) Langer (92) concludes from his work that the autonomic system may be over-irritated by roentgen ray exposure and cause a depressing effect. He uses this mechanism to explain the effect that X-rays produce at a distance from the field of exposure. He explains the so-called "stimulating dose" as producing a "depressing effect of actinic energy affecting an over-active or irritated autonomic nervous system."

Warren (69) considers the reports of changes in the vegetative nervous system as being controversial although there is much clinical material in its favor.

Lyman, Kupalov and Scholz (93) did some very thorough experimental investigation on the effect of irradiation

on the brains of adult dogs. They conclude that "roentgen rays may alter the function of the central nervous system but this action does not seem to be primarily on the cells of the cerebral cortex. After a high dosage in adult dogs there may be some lowering of excitability of cortical cells as determined by conditioned reflexes but this appears to be secondary to changes in blood supply." They discovered necrotic areas in the cortical tissue apparently due to obliteration of end arteries.

D. EFFECT ON PHAGOCYTOSIS AND ANTIBODIES

Pusey in 1904 (11) sums up the literature at that time by saying there are many exponents of the theory of increased phagocytosis due to X-radiation but no definite proof. Reiter in 1910 (94) records that radium radiation of the blood increased its phagocytic power. Chambers and Russ (95) found that both the opsonin and hemolytic complement were lost when the blood was exposed to alpha rays in vitro. The beta and gamma rays yielded negative results. The two complements changed at different rates when subjected to the radiation thus indicating the separate identity of the two. Simonds and Jones (35) in their experiments on rabbits found that the opsonic content and complement fixing power of serum of X-rayed rabbits did not differ a great deal from the controls. Knott and Watt in 1929 (96) observed loss of phagocytic power in polymorphs within 35

minutes and this loss appeared to be quite permanent. They considered that the decrease in phagocytic power was practically proportional to the intensity of the radiation and the area irradiated. There are so many factors involved that it is difficult to come to any conclusions and the whole subject of irradiation in vivo is so involved with theories of immunity that there is little agreement between the results of different investigators. Most of the conclusions are based upon statistically inadequate data. (97)

The intensity of the radiation used is a factor in determining varying results so far as antibodies are concerned. Hektoen (98) found that irradiation immediately following injection of sheep blood into white rats did not interfere with the production of hemolysins. He states that this is true as long as the radiation is not strong enough to be detrimental to the general health. When the radiation is begun several days before and the leucocytes are greatly reduced, the formation of lysin is restrained to a "remarkable degree." A single, eventually fatal exposure immediately before the injection of sheep blood, may prevent any formation of lysin for about the next 8 days. He draws some conclusions from his work to the effect that the "lymphocyte may be an important agent in the production of antibodies."

On the basis that the lymphocyte is connected with the resistance of the organism, quite a bit of work has been done on experimental tuberculosis. Here again, there are conflicting reports. Murphy (36) (98) and Morton (37) from their work with mice and guinea-pigs respectively, conclude that the lymphocyte is an important agent in the defense against tuberculoses and that by means of producing a lymphopenia in these animals the progress of the disease is accelerated. Weinberg (99) in 1920 attempted to duplicate these experiments, but found no difference in the progress of the disease in the tuberculous guinea-pigs which were irradiated and those used as controls. Spies (39) in 1931 concluded that irradiation of guinea-pigs with experimental tuberculosis did not retard the progress of the disease and did not definitely accelerate it.

In regard to other antibodies, Simonds (35) found that in rabbits which were treated 10 to 15 minutes daily for 3 weeks and then given a single dose of killed typhoid bacilli:

> "(a) Formation of agglutinins was appreciably lowered
> (b) Production of bacteriolysins for Typhosus B. was probably not greatly interfered with
> (c) The opsonin content and complement-fixing power of the serum did not differ a great deal from the controls."

Brooks (97) in 1936, after reviewing the literature, makes the following observations:

(a) Alexins: The data at hand neither prove or exclude the possibility that the alexin or complement content of the blood is increased by moderate X-irradiation.
(b) Hemolysins: There is no basis for concluding that hemolysins once formed are directly affected in vivo by irradiation of any kind.
(c) Precipitins: It is evident that X-radiation sufficiently heavy to cause serious injury to the reticulo-endothelial system, interferes with subsequent antibody production, but it has not been shown to have any marked effect on antibodies already produced.
(d) Agglutinins: On the whole, there appears to be reason to suspect that small doses of X-radiation given during the falling phase of agglutinin titer may give rise to a temporary increase. Irradiation before immunization leads to no change unless the dosage is large and then only to inhibition or prevention of agglutinin formation.
(e) Antitoxins: Data are statistically inconclusive.

## E. EFFECT ON MICRO-ORGANISMS

### 1. BACTERIA

"The earlier work on the effects of X-rays on bacteria was very largely negative, as might be expected when viewed in retrospect, if due consideration is given to the probable intensities of the radiation and to other conditions of the experimental work.....Franz Minck in 1896 (Zur Frage uber die Einwirkung der Rontgenschen Strahlen auf Bakterien und ihre eventuelle therapeutische Verwendbarkeit. Munch. Med. Wochensch. 5:101, 1896) was apparently the first to undertake a determination of the efficiency of X-rays as a bacteriocidal agency. He used a strain of the typhoid bacillus, streaking the surface of agar plates and exposing certain areas as long as 8 hours at a distance of 10 cm. to radiation from a Hittorf tube. Following an incubation period, no effect of the irradiation could be detected from the gross appearance of colony development. (100)

"While negative results were being generally reported between 1896 and 1897, indications were accumulating which were interpreted as showing indirect effects of radiation on bacteria. Thus, animals inoculated with the tubercle

bacillus were irradiated and compared with similarly inoculated and unirradiated controls with respect to disease development. In this way some positive indications were furnished." (100)

Rieder in 1898 (101) exposed six different organisms (B.anthracis, B.coli, B.diphtheriae, tubercle bacilli, streptococcus, Staphylococcus aureus and Vibrio cholerae) on agar and gelatin media. They were killed after exposures varying from 40 to 60 minutes and a distance of 10 cm.

In 1904 Pusey and Caldwell (11) published the following comments:

"The conviction cannot be escaped that the influence of X-rays per se upon bacteria is practically nil. It may be true that very long exposures with great quantities of energy produce an appreciable influence upon bacteria, but this destructive effect is so infinitesimal compared with the effect upon highly organized animal tissues that it may be regarded as nil and for all practical purposes might as well not exist. In vivo, it is quite different. When a suppurating ulcer is exposed to a sufficient extent to X-ray influence, unmistakable evidence of interference with the growth of the pus organisms is shown. The discharge changes from pus to a sero-fibrinous fluid and soon the ulcer becomes clean and free from evidence of contamination with pus organisms.

"I have repeatedly seen dirty, septic ulcers of carcinoma, syphilis and lupus become clean and sterile under the influence of the X-rays alone without the use of antiseptics and at times indeed under conditions most unfavorable for the maintenance of cleanliness."

In 1901, Rudis-Jicinsky (102) working on rabbits and guinea-pigs concluded that in alkaline media, tuberculosis is accelerated in its progress while in acid media, the process becomes inert. 40% of the animals treated by rendering their secretions acid and then irradiated were

cured of tuberculoses as proved by post mortem.

Pauli (103) applied .9 to 11.2 erythema doses in fractionated units to cultures of Pyocyaneus and Staphylococcus. When the temperature was between 37 and 41 degrees Centigrade there was an increase of 80% of Pyocaneus cultures and 100% in Staphylococcus cultures. Dozois et al (104) could find no alteration in the migration velocities, $P_H$ determinations or viability after X-radiation.

On the other hand, Wyckoff (105) killed B. coli and B. aertryke on agar surfaces by means of soft rays from a tungsten tube at 12 kilovolts. He found that they were killed in a linearly exponential fashion. He also showed (106) that wavelengths of 4 Angstroms to 0.5 Angstroms killed B. coli in semi-logarithmically linear fashion and that for "copper and harder radiations the biological action is proportional to their measured air ionization. Softer rays require a more intensely ionizing beam." Johnston in 1933 (107) found marked inhibition of bacterial growth when the bacteria were treated in the presence of Beck's bismuth paste and also when lipiodol was present. Peculiarly enough, he also found that after one hour exposure of bacteria in the presence of meat, there was also inhibition of bacterial growth.

Kempster (108) attempts to reconcile the opposite views of germicidal action of X-rays. Probably the experi-

mental differences are due to difference in media. The presence of inert substances or of living animal tissues evidently makes a pronounced difference in the effects of radiation on micro-organisms.

Newcomer (109) found that fluorescent crystals of fluorite increased the bacteriocidal effect of X-rays on water suspensions of E. typhi. He concludes that this is due to secondary radiation of 1800 to 2800 Angstrom units which is within the ultra-violet range and has bacteriocidal properties. Claus in 1933 (110) summarizes some of these methods of enhancing the effects. He mentions thorium, fluorescent dyes, high salt diet and caesium iodide as being synergistic in the bacteriocidal action of the rays. He experimented with the "heavy" salts, lead nitrate and potassium bromide. When large concentrations were used the effect was sharply increased.

"From the data now available it is well known that if any population of micro-organisms is exposed to radiation, inducing lethal effects, one may plot the percentage of survivals against the time of exposure and the results will appear in the form of a logarithmic or of an S-shaped curve.....An interesting physical interpretation of effects of this nature is the assumption that any organism or cell will die as soon as it has received the required, or critical, number of X-ray "quanta;" that is, the probability

feature applies to the number of quantum hits received, and not to the variability of the biological material." (100)

2. PROTOZOA

Little can be found in the literature concerning the effect of radiation on protozoal infestations. However, an interesting report is given by Yamaguchi (111) concerning his results in treatment of filariasis. He states that the X-rays kill the generative cells of the filaria and reduce the induration of the lymphatic vessels. He has had success in all the cases treated thus far.

3. FUNGI

It has been quite definitely shown by investigators that X-radiations exert a positive effect on plants but some of the evidence in regard to fungi has been less convincing. Perhaps in the cases where negative results were obtained, the intensity of dosage was too small. (112)

Neidhart (113) was among the first to report the lethal action of X-rays upon fungi. Wyckoff and Luyet in 1931 (114) found that yeast could be injured by X-rays without being killed. If the radiation was continued they might die after budding only once. There was no indication that small doses stimulated their growth in any way.

From the clinical standpoint, there is a great deal of evidence of the inhibition of actinomyces in vivo by X-rays and gamma rays. (115) (116) (117) (21)

Pusey (11) tells of the early treatment of favus and Gunnlaugur (118) in 1937 gave a report of treating 152 cases. However, there is doubt as to there being a direct effect upon the achorion Schoenleini. Rather the beneficial results are due to the epilation which carries source of nutrition and most of the organisms away. This is also true in the case of tinea tonsurans.

Reports of clinical benefit in other fungus diseases are found thru out the literature. McCormick (119) reported successful results after treating several hundred cases of dermatophytosis. Popp (120) describes his successful results in a case of Mycosis Leptothricia.

In general, then, various degrees of injury may be produced by gamma and X-rays.

"Yeast loses its ability to multiply with much smaller doses than are required for immediate killing. Such doses may merely retard division or they may cause the production of giant cells which have lost their ability to divide. Some cells may divide only once following irradiation." (112)

## IV PHYSICAL FACTORS INVOLVED IN RADIOTHERAPY

### A. X-RAY GENERATORS VERSUS RADIUM

The advantages of the X-ray are (a) that an even homogeneous dose may be delivered to a large surface and (b) the depth of penetration is readily controlled. The only advantage of radium is the ease of portability which, in reality, is no advantage where portable X-ray units are available. (121)

### B. TECHNICAL FACTORS

An important principle so far as dosage is concerned is that the radiation delivered into the diseased tissue be adequate and yet produce no ill effects in adjacent or superimposed healthy tissues. (121)

One must consider two factors of prime importance in the dosage to be used; i.e. quality which determines penetration and quantity which is the amount of radiant energy applied to the tissues over a certain period of time.

Quality is usually expressed in terms of wavelength. This is determined chiefly by the potential applied to the X-ray tube and screening by the filtering system. (122)

No filtering system is truly selective but simply tends to make the beam more homogeneous. Aluminum is usually chosen for low potentials giving the longer less penetrating wavelengths. In deep therapy, where the voltage is increased to 200 Kv. and above, copper is the more selective

filter. Thru the filtering process, the relative penetration of the remaining X-ray beam is increased by absorbing the less penetrating X-rays.

The effective penetration or depth delivery may be increased by increasing the potential and by increasing the filtration as outlined. It may also be increased by increasing the distance which lessens the dispersion and by enlarging the port which increases the scattering within the tissue. (121)

Quantity is measured in terms of roentgen units which have been defined in Section I, Page 6. In brief, the "r." is a physical unit based on ionization of air. The particular X-ray generator makes a difference in the dosage but should be calibrated in terms of "r." units for the purpose of accurately measuring the quantity of radiation administered.

The intensity or quantity depends on four factors: (a) It varies directly as the square of the potential (b) It varies directly as the milliamperage (c) It varies directly as the time (d) It varies inversely as the square of the distance. (124)

For superficial therapy, 60 to 80 Kv. should be used with little or no filtration as a rule. For intermediate depths, 100 Kv. with 1 mm. of aluminum and for deep therapy 200 Kv. with 0.5 mm. of copper and 1 mm. of aluminum may be

used. (121)

C. DOSAGE

Dosages which may produce epilation, sterilization, cataracts, dermatitis or other untoward effects, naturally should be avoided. It must be remembered that when intervals between treatments are short, the doses become cumulative and deleterious effects may be produced in that way. Rate of recovery decreases as dose increases. These effects do not appear immediately but a latent period intervenes. In view of these facts, anything more than a faint erythema should be strictly avoided in the treatment of inflammatory disease. Erythema doses are approximately 350 "r." with a superficially penetrating beam, 450 "r." with intermediate penetration and 600 "r." with deep penetration.

The following are the usual dosages used by (121) Dr. Howard B. Hunt of the Radiology Department of the University of Nebraska College of Medicine: Acute infections - 25 to 50 "r." twice a day. Total dose is not to exceed 450 "r." and parts which are not to receive treatment must be carefully shielded. Subacute infections require the same factors but with intermediate penetration. Chronic infections - 100 to 400 "r." with intermediate penetration. Usually one or two sittings are used in a week's time. The total dose should not exceed an accumulated erythema dose

so the treatment should not be repeated until after 3 to 4 weeks have elapsed.

In acute infections, the dose should be delivered to the pathological tissues and at least 2 inches beyond the edge of the visible lesion. (121)

## V RADIATION THERAPY IN SPECIFIC INFLAMMATIONS

### A. ACUTE INFLAMMATIONS

In general, for acute inflammations only a small dose of radiation is necessary because of the increased sensitivity of the tissues. Usually less than half an erythema dose is used and the more acute the condition, the smaller the dose required. (125)

1. FURUNCLE, CARBUNCLE AND OTHER PYOGENIC INFECTIONS:

The influence of irradiation on such lesions has been demonstrated by many different individuals. "Prompt, marked benefit is derived in most cases. Pain is relieved in about 24 hours, but in a small percentage of cases such relief may be preceded by a temporary increase in the pain." Irradiation has been found to be most effective during the early stages of the inflammation at which time most other methods of treatment have little effect. Many conditions respond with only one treatment but if not, it may have to be repeated at intervals, depending on the dose used. This may vary between 25 and 75% of an erythema dose. The quality of the rays may be adjusted according to the thickness of the lesion. The treatment may be given to weak and febrile patients without danger. Some other pyogenic conditions in which it has been found effective are cellulitis, phlegmon, peridental infection, adenitis, onychia, orchitis, epididymitis, mastitis and sinusitis. (126) Hodges sums up

the action of radiation upon carbuncles thus: "Irradiation certainly in the large majority limits the spread of the infection, lessens the pain, increases the drainage, shortens the course of the disease somewhat and I believe very definitely lowers the mortality." (127) In a large series of cases of pyogenic infections treated by X-ray, Hodges (127) states that his results have been "almost uniformly good." The following cases are given to illustrate his results:

> A white man, aged 27, non-diabetic. For 5 years he had suffered almost constantly with boils on the back of the neck. He had just spent 6 weeks in a hospital where boil after boil was lanced. Six weeks after the first roentgen treatment, his neck was healed and since then, after more than 5 years, he has not had another boil.
>
> In 1920, at a hospital staff meeting, one of the surgeons reported what he considered to be a hopeless, very large carbuncle on the back of a white man, aged 48, who was not a diabetic or a syphilitic. He had made a wide, criss-cross incision 6 weeks previously; the entire area sloughed out and at the time he reported the case, there was an enormous crater almost from scapula to scapula and only a watery discharge was exuding from the very thick edges of the carbuncle crater. The man had lost a great deal of weight, was weak and listless and appeared doomed. He was given about 150 r., 85 Kv. of unfiltered roentgen rays that evening. During the night, there was a very copious seropurulent discharge and within 24 hours there was some improvement in his general condition. The carbuncle was showing new granulation tissues and a healthier appearance. He went on to an uneventful recovery. This has not been an unusual but a fairly common experience. (127)

Dunham in 1916 (128) reported 67 consecutive cases of carbuncles. Lewis (44) reported 16 cases. Hodges (129) (45) (46) reported 34 cases. Wilcox (130) reported 28 cases of furuncles and carbuncles. Friedman (49) in 1934 after treating 114 cases of furuncles, 206 carbuncles and

354 cases of cellulitis and lymphangitis and 22 paronychias, reports "very gratifying results" and shortening of the course of the disease. Holzknecht (131) reported that 50 to 90% of his cases of pyogenic infections recovered almost immediately or else ran a much shorter course. In about 1/3 of his cases, the process was shortened and in another 1/3 good results were noted in 24 to 48 hours by crises. The remaining 1/3 consisted of those where there was fair improvement and those with complete failure. He cites Heidenhain's success in 243 cases selected where other treatments had failed (Roentgenbestrahlung Entzundung Arch. f. klin. chir. 133:624-655, 1924).

Carp in 1927 (132) after using various treatments in 153 cases of carbuncles is not as enthusiastic about X-rays as the majority of men reporting in the literature, but even he admits that it is an aid to conservative therapy in both small superficial carbuncles and in some large ones.

2. ACUTE PAROTITIS: Rankin and Palmer (133) compiled 78 cases of post-operative parotitis treated at the Mayo Clinic. Twenty of these were treated with radium. Only two, so treated, had to have surgical drainage as compared to about 50% in the patients not irradiated. Of this group, there was a mortality of 5% compared to 50% with the non-irradiated group. The technic used was the immediate application of four 50 mgm. tubes with 2 mm. of lead, 1 mm.

of brass and 0.5 mm. of silver and 2.5 cm. distance. A maximum exposure of eight hours and an interval of eight hours were used with a total mgm. hour dose of 6605. Minimum dose consisted of two 50 mgm. tubes giving a total dose of 800 mgm. hours in two applications. After 48 hours from from the beginning of the treatment, there is rapid improvement and no tendency to suppuration. Temperature returns to normal and the patient is usually well after the fifth day.

Friedman (49), Robinson and Spencer (134) and Allen (135) using roentgen rays, definitely agree as to the favorable results. Early treatment is important for the best results, however. Allen reports 26 cases and states that the pain is relieved in 3 to 12 hours, and that after 2.6 treatments on an average, the major symptons have subsided.

The following case is one of those treated by Dr. Howard B. Hunt at the University of Nebraska College of Medicine. It serves to show the beneficial results obtained even though the case had progressed for three days before roentgen therapy was resorted to.

White female, age 64, clinical diagnosis of acute parotitis with concurrent diabetes mellitus and acute infectious arthritis. A large, soft, tender mass, 3x7 cm. at the angle of the right jaw in the parotid was noted Nov. 8 and the usual medical treatment was applied. A dose of 79 Kv., 5 ma., no filter, 30 cm. distance, 80 r. was used every day for four days. A total of 320 r. was delivered.

During this time, the swelling receded and the symptoms

were alleviated. (136)

3. ERYSIPELAS: In 1932, Widmann (137) reported a series of 97 irradiated cases and 97 control cases with outstanding results. Although there were six deaths in the control group and ten in the irradiated group, the average duration of the disease was only five days in the irradiated ones while it was 10 days in the other cases. In 56% of the cases treated with X-ray, the temperature fell to normal in less than three days. Best results were obtained when the patients were treated early and no cutaneous or systemic reactions were noted even in weak and very febrile patients. He advises no local application to the skin with the possible exception of cold boric acid packs. Irrigation to the eyes may be given. Wilcox (130) reported good results in four cases.

Hodges in 1936 (138) reports that although the usual course of erysipelas cases is 8 to 14 days in duration, under roentgen ray treatment the course is shortened to from one to three days. Friedman (49) after treating 39 cases concludes that the spread of the local lesions is definitely checked. Desjardins (126) states that if the erysipelas does not complicate diabetes or nephritis, it responds well, especially in adults. For some reason, young childred often are not benefited.

Case History from University of Nebraska Hospital (139)

White, male, age 69 with a diagnosis of pernicious anemia and bronchopneumonia developed a chill and a temperature of 104.4 on Jan. 23, 1938. Shiny, brawny edema of the nose and cheeks. Erysipelas was the diagnosis and was treated immediately with wet packs and sulfanilamide gr. X--q.i.d. The following day, roentgen therapy was instituted. 54 r. were administered over an area of 10x10 cm. at 100 Kv. 18 ma. 37 cm. distance with no filtration except the tube wall (which is equivalent to 0.25 copper) in one minute's time. On the morning of the 25th of Jan. his temperature fell and his general condition was much better although the face was still red and the eyelids swollen. The next day, the induration had subsided and the erysipelas was pronounced clinically well.

It is interesting to note that the above case was successfully treated with X-ray although complicated by pernicious anemia and with no bad effects.

4. MASTOIDITIS AND OTITIS MEDIA: Schillinger in 1932 (1) relates that as early as 1924 he noticed favorable results after mastoids had been exposed to X-rays for the few seconds necessary to register on a photographic plate in the course of diagnosis and recheck. He then started administering a 25% erythema dose using a fiber filter and a focal distance of 16 inches. In over 85% of his cases, there was an apparent change within 24 hours after exposure. There was lowered temperature, cessation of pain, absence of insomnia, lessened quantity of discharge and a change from purulent to muco-purulent. Three to four exposures were sometimes necessary.

In 1938 (140) after using the same treatment in quite a group of cases, he gives the following as possible contraindications for roentgen therapy: (a) Edema over the mas-

toid as caused by a thickened periosteum or a perforation of the cortex (b) Transient edema in the region of the emissary vein, indicative of perisinus abscess or sinus thrombosis (c) Torticollis, indicative of filtration of infection into the neck thru the tip cells (d) Swelling at and below the mastoid tip, indicative of necrosis and perforation of the tip with gravitation of pus into the sheath of the sterno-cleido-mastoid muscle (e) Failure to induce the "syndrome of favorable action" described in the above paragraph (f) Signs and symptoms of invasion of the blood stream or of irritation of the dura or of the labyrinth (g) Diabetes with roentgen evidence of bone destruction.

In regard to an otitis media, he has found that roentgen therapy is practically the only available effective method of preventing the otitis from progressing to a mastoiditis. He advises 20 to 50 r. at least by the seventh day of suppuration in otitis media and to be continued at 2 to 3 day intervals until the danger is past.

Goosmann as early as 1922 (141) treated 10 cases of post-operative mastoiditis which still complained of pain and discharge. After from 2 to 4 exposures of a 50% erythema dose thru 3 mm. of aluminum, he noted distinct and rapid improvement.

Ross in 1932 (142) reported 31 cases of acute mastoiditis and 7 subacute which were treated and good results obtained.

Dosage used was 80 Kv.,5 ma., filter of 5 mm. aluminum and 5 mm. of felt next to the skin, distance 13 inches, time 6 to 7 minutes. Treatments ranged from 7 to 12 in 5 to 10 days, usually given every 8 to 12 hours. The pain stopped after 3 to 5 exposures; tenderness was relieved after 5 to 7 treatments, and the discharge temporarily increased for from 2 to 4 days then began to lessen rapidly. The subacute required a few more treatments and a longer period of time.

Friedman in 1934 (49) reported "remarkable improvement and cures" in 21 cases of mastoiditis. Lucinian (143) reported 9 cases of which 7 recovered without operation and 2 required mastoidectomy.

In a series of 31 acute and 8 subacute cases of otitis media Lucinian (143) reported no recurrences or complications, while in a series of unselected cases not treated by X-ray, there were 5 perforations, mastoiditis in 9, mastoidectomy required in 5 and tympanotomy in 11. Pain was relieved by the first X-ray exposure. Temperature dropped gradually to normal (10 to 15 days). There was an initial increase in discharge and then a gradual decrease. When perforation was present, healing occurred in 2 to 3 weeks. Hearing improved in 24 to 48 hours and was restored to normal.

Levin (44) in 1933 reported 29 cases of otitis media in children with beginning symptoms of mastoiditis. From

1 to 3 irradiations brought about a complete subsidence of symptoms except in 2 cases, which finally required bilateral mastoidectomy. No deleterious effects were noticed in any of these cases. The following is a case from his series.

"Case 4. A. H. aged 2 years. Developed otitis media in the winter of 1928 requiring paracentesis. The temperature fluctuated between 100 degrees F. and 104 degrees F. for 2 weeks. Paracentesis was repeated on six occasions following which the temperature would remain normal for only 24 hours. During the periods of high temperature, the child was fretful, apparently in pain and unable to sleep. The otologist advised bilateral mastoidectomy but consented to one treatment of X-ray and a 24 hour delay in operation. Twelve hours after X-ray therapy, the temperature was normal. There was apparently no pain. The ears discharged approximately the same as before. Ten days later the discharge ceased completely. No further attacks occurred.

5. LYMPHADENITIS: Rosenberg (145) treated 80 cases of acute cervical lymphadenitis secondary to infections of the upper respiratory tract. No auxillary treatment was used. He exposed them to 260 r. at 150 to 180 Kv. and if a second treatment was required, it was given after 5 to 7 days. 85% of his cases subsided without suppuration or any need of surgical intervention. There was rapid resolution or "break-down" and relief of pain and discomfort. In no case, were there unfavorable effects. All of the 80 cases reported were children under 7 years of age. He suggests that very young children should have the dose reduced accordingly. Levin in 1933 (144) reports 21 cases of severe lymphadenitis and states that the results

were strikingly beneficial. The duration of the inflammatory process was definitely shortened.

Pfahler and Kapo in 1934 (146) reviewed 333 cases of cervical adenitis. Out of the 159 that returned for observation after the first treatment, only 7 were unimproved. The remaining 152 showed from 50 to 100% improvement. During the last 5 years, they treated 92 cases. Of these, every case was either greatly improved or cured. 300 r. were used at a single dose and from 2 to 4 treatments were necessary for cure. Friedman (49) in the same year, reports 101 cases and concludes that if seen early only one treatment is necessary. If far advanced, the dosage may be repeated once or twice at intervals of a week.

6. GAS GANGRENE: There have been comparatively few cases treated by radiation and reported in the literature. Those reported indicate very good results. Kelly in 1933 (147) reported 6 cases, all of which recovered. In 3 of these cases, amputation was deferred in order to observe the effect of the X-ray. After the series of treatments, amputation was unnecessary. Faust in 1934 (148) reported 7 cases. All of these recovered with the exception of one. In this case, death was due to the shock of operation and the delay before X-ray therapy was begun. In these cases, serum for B. Welchii and B. vibrion septique was also used although in 2 cases the organism was B. Claustridium

tertium.

Up to the time of Kelly's report in 1936 (43), he had treated 56 patients. In his first series of 8, 2 with trunk involvement died. In his second series of 32 cases, all 8 with trunk involvement recovered and there were 5 deaths among those with only extremity involvement. Of these 2 were apparently cured and died accidental deaths. Two others had received only to doses of X-ray and failed to rally after amputation. His last series of 16 patients was very successful. All lived and 5 had no serum. Two had amputation but recovered. He concludes:

(a) X-ray therapy is indicated in gas gangrene in both extremity and trunk cases.

(b) Therapy should be started as soon as the disease is suspected and given thru out the course, twice a day for at least three days.

(c) Amputation seems a disadvantage as long as the gas bacillus is present.

He advises the use of X-ray in all cases and also the use of serum unless there is some contra-indication. Tetanus anti-toxin should also be used. Local surgery and treatment may be used as indicated. Amputation for gas bacillus infection, as a rule, should not be done.

Case History from University of Nebraska Hospital. (149)

"White, male, age 12, sustained a compound fracture of the left forearm which was badly contaminated. The following day, he was given combination tetanus and gas bacillus anti-toxin (10,000 units). His arm was manipulated and immobilized in plaster. On the third day following the

fracture, the hand and fingers were found to be cold. The arm was amputated just below the elbow and then treated with X-ray. Radiographic study showed extensive mottling of the soft tissues by gas--mostly below the elbow and some streaking upward to the shoulder. A total of 424 r. was given in four doses ranging from 48 to 108 r. in 3 days' times. One mm. of aluminum was used as filter. On the second day of treatment, the radiographs still showed extensive distribution of gas below the elbow and some gas above with slight swelling in the lower 1/3 of the arm. Gas bacillus antitoxin (10,000 units) was again administered. The temperature dropped noticeably and continued a gradual decline to normal. The fourth day following the initiation of the X-ray therapy, radiographs revealed that accumulations of gas in the upper arm had disappeared and there now remained some residual gas in the lower 1½ inches of the stump. (149)

7. MASTITIS: Pfalz in 1934 (150) reported his results after experimenting with mastitis in guinea-pigs. Staphylococcus aureus was the organism used and mastitis was produced in both breasts. One was irradiated and the other used as a control. He found that suppuration was usually prevented and the course was shortened. Interesting enough, is the fact that in unilateral mastitis, irradiation of the normal side often caused healing reactions in the affected side.

He then reported 41 cases of puerperal mastitis in human patients. He concludes that X-ray treatment proved definitely superior to other forms of treatment. No ill effects were seen and there were no disturbances in lactation.

Margraf in 1936 (151) reported results in 118 cases of puerperal mastitis. In 71 of these, treatment was started

within 24 hours and there was spontaneous healing in 92% of them as compared to 71% in 127 non-irradiated cases. Cases in which irradiation was begun after 24 hours, there were spontaneous cures in 81%. Auxillary treatment consisted of pumping the breasts dry before radiation and elevation by means of bandages after treatment. In most cases, after 24 hours, there was marked general and subjective improvement. Pain and redness disappeared. The breasts were regularly emptied mechanically and the milk was used after boiling.

Friedman (49) after treating 17 cases of breast abscess says that "considerable destruction of tissue may be avoided if treated early."

8. PNEUMONIA: Powell (152) treated 30 cases of broncho-pneumonia with very good success. Carl Fried in 1937 (153) reported his results after treating experimentally-produced broncho-pneumonia. They were severe and hemorrhagic in type with a tendency to purulent exudation and abscess formation. Irradiation was administered 10 to 24 hours after injection. The control animals macroscopically showed complete hepatization of the lungs. Lungs of the radiated animals appeared almost normal with only scattered areas of hepatization. Microscopically, congestion, edema, infiltration and abscess formation were distinctly less.

Powell (154) irradiated 47 cases of lobar penumonia in

various stages of the disease. Supportive treatment was given but serum was omitted. Crisis occurred usually within 24 hours but more than half recovered by lysis. Four developed empyema but two of these probably had it at the time the first radiation was given. One patient developed a bilateral otitis media with mastoiditis and another meningeal symptoms. Out of this series, there was only one death. A 50% erythema dose was used and those that did not respond promptly were given a second treatment 24 to 48 hours later on the field opposite the first.

In a later report, he (152) describes his results in 105 cases of acute lobar pneumonia. Routine supportive treatment was used in all cases and serum used in only three. There was a mortality of five (about 5%). Two of these patients had received serum as auxillary treatment. He noticed that when the disease was in the congestive stage, as determined by radiographs, radiation sometimes caused the disease to spread and the course might be prolonged. He considers leukopenia to be a contra-indication to roentgen therapy. Within 36 to 48 hours after one treatment, if the temperature and leucocyte count have not dropped to normal, a second treatment is given to the field opposite the first.

Desjardins (126) considers roentgenotherapy ineffective in cases where the pneumonia exudate is becoming organized.

9. LUNG ABSCESS: Finestein and Poppe (155) reported results in a series of 30 patients. Twenty-five of these were uncomplicated lung abscesses. Four were gangrene cases and one was an abscessed cancer. The cancer case and three of the gangrene cases failed to recover. In 22 cases there was complete recovery without complication or relapse within 5 months to a year after treatment. X-ray films of these cases revealed scar formation and abscence of abscesses.

Porchownik (156) reported both subacute and chronic cases of pulmonary gangrene resulting from influenzal pneumonia. He concludes that patients in which the normal defense reactions are intact, may be completely cured by means of X-ray.

10. PERTUSSIS: Tuschilkin (157) reported 70 cases of whooping cough treated with 10 to 15% erythema dose at 140 Kv. with 3 mm. of aluminum. This dose was delivered every other day and in some cases every day. The anterior and posterior chest walls were exposed alternately, covering an 8 x 12 cm. field. In 36 cases, the results were good. In 23 excellent results were observed and in 11 cases only slow improvement was noted. Samuel in 1929 (158) reported good results using practically the same amount of radiation in intervals of 3 to 7 days depending upon the severity of the case. The average number of treat-

ments was 3 to 4 directed to the anterior chest wall. A small cone was used to direct the rays to the hilar region. Results consisted of prompt relief of paroxysms of both vomiting and coughing. The usual extensive course of the disease was definitely shortened.

Before this, Smith, Bowditch and others (159) reported an analysis of 850 cases treated by X-ray. They apparently made careful studies of their cases and were very enthusiastic about their results. Their mortality in the series was only .3% as compared to 6.4% for the state of Massachusetts. They make the statement that "roentgen ray treatment is the most uniformly satisfactory means of treating whooping cough."

In the same year (1925) Faber and Struble (160) report a very thorough study of a series of 44 cases of which half were given irradiation on three occasions at intervals of 3 to 4 days over the anterior and posterior aspects of the thorax in doses ranging from 56 to 168 E.D. units. The other 22 cases were treated with antipyrin. Making records of the paroxysms and incidence of vomiting, they discovered that the two groups showed quite parallel results so far as rate of progress was concerned, but the control group made a much better showing. Apparently, the roentgen therapy had been given during the period of natural decline of symptoms.

Desjardins (161) after surveying the literature states that although Faber and Struble reported only a small group it is only fair to conclude "that the therapeutic value of of Radiotherapy in pertussis is uncertain and at the present time (1932) stands unproved."

11. SINUSITIS: Osmond (162) reported 12 cases, 10 of which were in the acute purulent stage while the other 2 were in the acute catarrhal stage. His attention was first brought to the idea of X-ray treatment for sinusitis when he found that after making radiographs for diagnosis of suspected frontal sinusitis, there was relief from pain in the forehead. All the cases he treated recovered in from 3 days to 3 weeks. The relief of symptoms and cessation of pus were coincident with the X-ray therapy. He offers this as a method of preventing the progress of acute catarrhal sinusitis to acute purulent or from acute purulent to chronic sinusitis.

Desjardins (161) after reviewing a few other reports, believes that there is an indication (in 1932) for X-radiation in inflammatory conditions of the nasal and accessory sinuses and that they respond in much the same way as do other inflammatory processes.

B. CHRONIC INFLAMMATIONS

For chronic inflammations in general, a larger amount of irradiation at one sitting is necessary than for the

acute and the number of exposures must be increased in order to be effective. The dose usually given ranges from 50 to 80% erythema dose or about 350 to 500 r. delivered at 130 to 140 Kv. with a filtration designed for the amount of penetration desired. (28)

1. CHRONIC SINUSITIS: Butler and Wooley (163) in their article published in 1934, describe the results obtained by Dr. Larsell in making histological studies of the infected sinus membranes of cats after irradiation. The membranes became greatly reduced in thickness which appeared to be primarily due to an early destruction of lymphocytes. "There was no evidence of injury to the cilia, epithelium or cellular elements other than the lymphocytes." They report 700 clinical cases of chronic sinusitis, 450 of which were followed. 36% were entirely relieved, 55% were definitely improved and 9% were only slightly improved or not at all.

Smith and Nichel (164) have treated 25 cases. They divide them into three groups. In the first group, having sinus symptoms and watery nasal discharge, there was 100% improvement. In the second group, having had previous operative procedures, there was 87% improvement and in the third group, having heavy catarrhal post nasal drip, there was the least improvement.

Butler and Woolley recorded 5 case histories. The fol-

lowing is illustrative of their results. (163)

Case 1, male, age 45, was referred by his rhinologist for treatment. His symptoms dated back 4 years, during which time he had failed to respond to routine therapy. Radiographs taken at this time showed bilateral thickening of the membranes in the antra, with hazing of the ethmoids also. The antra were irradiated and the patient failed to return until one year later. He reported decided improvement but still had some discharge. The membranes, although reduced, were still definitely thickened. The ethmoid fields were still hazy. A second treatment was given over the antra and this time the ethmoid areas were also included. A check-up 6 weeks later showed a definite improvement and no further treatment was given. Three months later he returned for treatment of a carbuncle and reported that he had had no further evidence of sinus involvement. A film made on that date showed the sinuses to be clear.

2. ACTINOMYCOSIS: Many observers have noted the beneficial effect of radiation in this condition. There seems to be a "unanimity of opinion that surgical drainage together with roentgen therapy can bring about a complete cure in actinomycosis without the administration of iodides." However, when iodides are given in large doses and for a long period of time, they may also be very effective. (21) Smith (165) considers X-ray to be a distinct advance in the therapy of actinomycosis and states that iodides may be used in conjunction because of possible additional benefit. He advises comparatively large doses.

Bray (166) reported two cases treated with radium. Stewart-Harrison (117) reported 30 cases treated with X-ray. Twenty-two of these were successful. He advocates a protracted fractional method of irradiation. Smith (165) cited 9 case histories to illustrate the type and effectiveness of

roentgen therapy. The following is one in which potassium iodide was not used.

Case 1. (No. 11570) male, aged 66. Three weeks before admission, the patient had had two lower left molars extracted. Immediately thereafter, his left lower jaw began to swell and became tender, hard and painful. On incision, typical actinomyces were found. He received 800 r. (200 Kv. p., filter 0.5 mm. Cu. plus 4 mm. celluloid) in daily doses of 200 r. When seen again a month later, he had improved markedly and the wound had closed. He was then given 400 r. and 200 r. on the following day. Six months later, he was still in excellent condition. Nineteen months after entry when last heard from, there had been no recurrence.

Dyes (116) in 1934 reported 33 cases in which he combined K I and roentgen therapy. He used dosages of 40 to 100% E D. per focus at 180 Kv with 0.5 mm. Cu. plus 3 mm. al. All of these cases recovered in from 3 to 32 weeks.

3. BLASTOMYCOSIS AND OTHER FUNGI INFECTIONS: Desjardins in 1925 (167) stated that radio therapy was the treatment of choice in superficial blastomycotic infections.

Howe and Schmidt (168) cited 2 cases of broncho-mycosis successfully treated by X-radiation. He used a $3\frac{1}{2}$ inch spark gap, 40 ma., 20 inch distance, exposing the chest for 3 to 9 seconds every 5 days. In one case the cough and sputum disappeared 23 days after the first exposure.

Hodges (138) recommends roentgen therapy for both blastomycosis and sporotrichosis using K I therapy in conjunction. Desjardins (126) states that "at the present time (1935) radio therapy is the most potent single method"

of treating both actinomycotic and blastomycotic infections. When they are superficial, the majority may be cured by this method. When the disease is extensive and involves the intestine or lungs, X-radiation may bring about an occasional cure but in the majority of cases the prognosis is poor.

4. TUBERCULOSIS:

(a) Pulmonary

After reviewing the literature which is very extensive, Desjardins (161) in 1932 concluded that moderate dosages "may retard the evolution of tubercles, diminish the tendency to caseation, increase the proliferation of connective tissue and hasten calcification." This is most likely to occur in the early infiltrative stage of the tubercles in the chronic productive form of the disease. He considered that roentgen therapy may be distinctly valuable in "well-selected cases and under proper conditions." He advised, however, that it be restricted to institutions where other well-established methods of treatment may be used at the same time.

Ferretti (169) reported his method of treatment in 1934. He has treated 24 patients. It is too soon to judge as to permanent results in these cases but no unfavorable incidents occurred. All gained in weight and subjectively were improved also. Cavitation decreased in

one patient.

Von Vasshegyi (170) after treating 25 cases found that "X-ray treatment of ambulant cases of productive pulmonary tuberculosis was free from danger and often resulted in improvement." Higher than subfebrile temperature and poor general condition as in exudative tuberculosis or miliary tuberculosis are considered to be contraindications.

Wilkinson (171) reported in 1921 that he had been treating pulmonary tuberculosis for the past 7 years and that most of them were decidedly benefited. He considered that the arrest of the disease was "complete or partial in proportion to the fibrosis and calcification of the chest lymph glands."

(b) Adenitis

Reeves (55) treated 141 cases of tuberculous cervical lymph nodes. He found that the best results were obtained in patients having tuberculous sinuses. Of these, 76.8% were apparently cured. On an average, it required a period of 8 months for a cure. He used small doses in intervals of less than 3 weeks and found that these irradiations tended to shorten the course and favor resolution.

Desjardins (8) advises that surgical treatment in this condition be confined to incision and drainage and sometimes curettage of caseating or suppurating

contents. He uses both X-ray and ultra-violet radiations. The entire body should be exposed to ultra-violet every day. X-radiation should be given every 4 weeks and not over an 80% E D.

Reeves (55) disagrees somewhat as to the value of aspiration. He states: "Our experience has shown that aspiration alone has little or no therapeutic value in cystic or in fluctuating tuberculous lesions in the neck." In his method of treatment, he attempt to bring about resolution of the process without softening and therefore used smaller doses than Desjardins--averaging about 1/3 E D.

Many other radiologists affirm the successful use of roentgen rays in this condition. (54) (172) (173)

(c) Peritonitis

Mayer (174) (175) believes that light therapy always deserves a trial before any other type. He considers the serous exudative form to be most responsive to light radiation. If other measures are unsuccessful, then X-ray may give favorable results. There may be reactions at the first with slight fever and malaise but this will not interfere with continuance of the treatment. The results obtained with roentgen therapy are difficult to evaluate and he considers that this treatment should "not be stressed as particularly valuable" in this condition.

Desjardins (8) on the other hand, is more enthusiastic. He considers radio therapy to be the treatment of choice but also considers surgical measures such as abdominal paracentesis to be necessary in some cases. He advises "exposure of the abdomen thru both anterior and posterior aspects once every 4 or 5 weeks, supplemented by daily exposure of the entire body to gradually increasing doses of ultraviolet rays."

(d) Eye

Many articles in the literature have shown by clinical reports that tuberculous conjunctivitis and keratitis are amenable to the roentgen ray. There have also been many reports of cure in tuberculous iritis. In general 50 to 75% E D. of rays of medium wave length thru 4 mm. al. and repeated once a month is sufficient. (8) Mayer (174) agrees with this, stating that it is also effective in tuberculosis of the cornea.

In 1936, Negru and Michail (176) cited results on 21 patients with tuberculous iritis. Seventeen of these showed miliary tubercles with the biomicroscope and after treatment these all disappeared. Three cases of diffuse iritis were not influenced. Two cases with confluent tubercles tending toward necrosis and perforation responded promptly. There was improvement in 7 to 10 days and healing in 3 weeks.

In regard to the possibility of cataract production after irradiation, Desjardins (177) in 1932 concluded that according to the literature up to that time, there was little danger of cataract production as long as no inflammation was produced in the conjunctiva. The lens and conjunctiva are considered as having about the same sensitivity to radiation.

(e) Uro-genital Tuberculosis

Mayer (174) makes the statement that this condition deserves a trial of irradiation in combination with other measures such as ultra-violet light and antiseptics, if these have not succeeded by themselves. He is of the opinion that roentgen therapy has only occasionally proved of value in this form of the disease and that usually in the healing of fistulas.

Lazarus (178) tells of 47 patients with renal tuberculosis who were treated with X-ray after nephrectomy. Ultraviolet radiation was also used. There were only 2 cases with persistent fistulas. He considers that after fistulous tracts have formed, ultraviolet and X-rays have no particular advantage over other types of treatment. He treats tuberculous cystitis by instillations of colloidal silver into the bladder and then irradiation with X-ray.

Desjardins (8) in regard to cystitis states that the many reports on this condition "lead one to think that periodic exposure of the bladder to a small dose of

roentgen rays tends to reduce the spastic phenomena, relieve symptoms and hasten resolution of the inflammatory deposits." There is some division of opinion as to the treatment of tuberculous epididymitis. "When the lesions are extensive, however, prompt surgical measures, followed by radio therapy and helio therapy, undoubtedly are indicated." (8)

The difficulty of diagnosis and the mortality following operation of tuberculosis of the female genital structures has brought many surgeons and physicians to try radiation. There are several reports indicating favorable results. (8) Bickenbach in 1936 (179) reported in his cases:

(a) Operation alone 70% healing--24% mortality
(b) Operation & Radiation 67% " --19% "
(c) Radiation alone 78.8% " --11% "

He mentions 2 possible contra-indications to roentgen therapy; First, when there are large movable pus sacs and Second, when there is a massive mixed infection or septicemia. Of course, it is contra-indicated if sterility is undesirable. He states that early in the course of X-ray treatment there is increased appetite, gain in weight, prompt relief of pain. Regression of palpable masses requires up to 6 months. However, relapse frequently occurs requiring a new series of treatments or surgical removal.

(f) Bone and Joint Tuberculosis

Here again there is some disagreement as to the relative merits of irradiation and surgery. The decision between the two may depend chiefly on economic factors. In European countries when surgery is resorted to many surgeons advise supplementary irradiation with X-rays and sometimes ultraviolet rays also. This has never been thoroughly tested in this country. Usually repeated treatments over 6 months to 2 or 3 years are required for resolution of the tuberculous processes and repair of the affected bones or joints. Ultraviolet baths may be used daily to supplement the treatment. (8)

Mayer (174) considers X-radiation to be useful in cases of involvement of small and superficial bones, but again is not enthusiastic about this method.

Southard (180) reported 11 cases including spine, femur, hip joint, foot, ankle, hand, ilium, humerus and sternum. All of these had been operated upon before treatment with X-ray. Six of them had been operated 11 times. After radiation, discharge ceased, sinuses closed and bone repair progressed.

5. UNRESOLVED PNEUMONIA: The response of unresolved pneumonia to radiation has been outstanding in its rapidity and successfulness. Quimby and Quimby (23) in 1916 stated that "no pathological process in the body responds quicker

to an X-ray exposure than the non-resolution following pneumonia." They cited 12 cases. Edsall and Pemberton cited 5 cases..(53) Krost (24) cited 12 more and Merritt and McPeak (26) in 1930 reported 7 cases. They remark concerning the rapidity of the parenchymal resolution and mention that the hilar lesions are slower to respond.

6. GONORRHEAL INFECTIONS: Henry (181) treated 16 cases of chronic gonorrheal infections in women with good results. They ranged in chronicity from 2 to 9 years. All had edema and erosions of the cervix. Six had received douches consisting of iodine, salt, soda and lysol. Glycerin and carbolic applications had been used twice a week as well as sitz baths. After X-ray therapy, the erosions disappeared, discharge became thin and slight and there was marked improvement in general health. Within 3 months following radiation negative smears were obtained. The menstrual cycle returned to normal in from 6 to 12 months.

Liberson (182) treated 35 cases of gonorrheal arthritis and osteo-arthritis in males. Only 3 of these failed to obtain some relief from pain before the end of the second week of treatment. Twelve of them showed recurrence. He recommended that X-ray be used only in the most severe cases of arthritis. He did conclude that the rays were uniformly effective in gonorrheal

periostitis.

Carl Fried (57) after reviewing the cases in the literature of gonorrheal arthritis found that most writers report relief of pain within 24 hours. He recommends the use of roentgen rays particularly in the early stage so that splints may be left off and diathermy, massage, etc. may be used also. The genital gonorrhea must, of course, be treated at the same time.

Garland (12) in 1935 reported 30 cases of gonorrheal arthritis in which 80 joints were involved. He considered 13 cured after treatment, 15 much improved and 2 not improved. Treatments per joint were from 1 to 10 and averaged about 5.7 per patient.

7. ARTHRITIS DEFORMANS: Pannewitz (183) treated 1,507 patients with arthritis deformans over a period of 6½ years. He reported the statistics on these cases in 1933. He had 76% improvement in arthritic spines, 87% in lower extremities and 89% improvement in the upper extremities. He is certain that the duration of the disease at the time of treatment has a definite effect on the results. The duration is approximately inversely proportional to the results. In those of one month standing, 85% were improved; while in those of one year duration, 50% were improved. Out of 140 cases in which radiographs were taken, 65% remained stationary while the remaining

35% showed continued progress of the disease. The radiographs and subjective symptoms did not always run parallel. He suggests a possible cure in 46% of the cases.

Fried (57) treated 34 cases in men and 101 cases in women. He found that most of them required only one series of irradiations. Joints of the trunk required on the average 4 irradiations, the small joints of the extremeties 3, the knee 3, the hip 4 and the shoulder 4. The small joints improved most rapidly in 6 to 7 weeks. The hip joint showed the highest percentage of failures. Almost 1/3 of the knee joints were entirely cured. Almost 2/3 were much improved. In 10% of the cases, another attack occurred between 6 months and 2 years from the time of treatment.

8. ARTHRITIS: Langer (184) is of the opinion that the vegetative nervous system has much to do with arthritic symptoms. In a series of 363 patients, 86 showed marked symptoms of vegetative nerve disturbance. Twenty-three of these he gave local and paravertebral irradiation. In 63 he irradiated the corresponding ganglia and nerves. This often made them so comfortable that local radiation over the joint seemed inadvisable. Only 25% responded with little improvement. He used skin temperatures as an index of vegetative nerve disturbance.

Garland (12) reported 3 cases of chronic infectious arthritis, 2 of which became free of symptoms and 7 cases

of chronic hypertrophic arthritis, of which one became free of symptoms and 4 were improved.

Lattman (185) in 1936 reported 20 cases of subacromial bursitis. Fifteen were relieved of pain in 24 to 48 hours after the first treatment. One failed to be relieved after 2 treatments. Number of treatments necessary varied from 1 to 3.

Huc and Aime (186) reported the use of roentgen rays in several hundred cases of peri-arthritis of the knee joint with great success. They used 75 to 125 r. at first, increasing the dose to 200 to 250 r. Seven to 12 treatments were given over a period of 3 to 4 weeks. Usually after the fourth treatment, there was improvement. After about 2 months from the first treatment, joint function became normal.

9. OSTEOMYELITIS: There are a few articles in the literature in regard to osteomyelitis. Philips and Finkelstein (187) reported 50 cases in 1921. Of this group only 3 showed no effect and in 8 there were relapses. He described the benefits of radiation thus: (a) It hastens sequestration (b) Closes sinuses and (c) Relieves pain, muscle spasm, temperature and malaise.

Rona (188) treated 27 cases of periostitis and osteomyelitis with favorable results. All symptoms of pain, swelling and suppuration were relieved. Sequestra were loosened

and eliminated. Complete healing followed. He states also that the osteoplastic function of the bone was increased after irradiation.

10. EAR, NOSE AND THROAT INFECTIONS: Beattie (189) noted the effect of taking X-ray films of ears and mastoids in cases of otitis media. He then treated 14 cases of chronic otitis media and after from 1 to 3 treatments, considered that he had 9 cures and 5 improved. Eraner and Weiner (190) in 1934 reported 15 cases of otorrhea following mastoidectomy with complete cure. He used doses of 50 r. bi-weekly for 2 to 3 months directed at the external auditory meatus thru 0.5 mm. cu. and 1 mm. al. Lucinian (143) treated 11 chronic cases of otitis media with good results and no recurrence or complications for 3 years. He used 15 to 20% E D. and found that in chronic cases it required from 3 to 6 treatments.

Boccioni (191) treated 30 cases of chronic hypertrophic tonsillitis and 32 cases of chronic cryptic tonsillitis. He found the results to be exceedingly satisfactory in most cases. In 6 cases there was recurrence in attenuated form. In 3 cases the treatment was unsatisfactory and tonsillectomy had to be performed. The hypertrophic form reduced in size and the inflammatory reaction disappeared. The cryptic form showed disappearance of both crypts and inflammation. He used 55 to 110 r. for 5 to 10 applications thru 0.5 mm.

cu. and 3 mm. al. with the rays centered on the angle of the mandible. Sordello (192) reported 5 cases of chronic tonsillitis treated with notably good results and 13 cases of laryngeal tuberculosis. In these latter cases, the dysphagia and dystonia retrogressed rapidly as did also the lesions, in some cases, to complete disappearance. Hundemer (193) reported 78 cases of which in 2/3 the recurrent sore throats were stopped. In the others, the attacks were reduced in frequency and severity. Only 5 had subsequent operations. He found that the soft hypertrophic type responded the best and the white fibrous type the least. Dubowyi and Olschanowskyi (194) reported 64.2% cures in 163 cases, 31.6% improvement and 4.2% failures. Schulte (195) reported 86.1% cured, 11.9% improved and 2% failures in a series of 794 cases.

11. OPHTHALMOLOGICAL INFECTIONS: In the early history of roentgenotherapy, trachoma was treated with apparent success. (19) Lane (196) in 1924 compiled over 100 cases of trachoma treated by radium with good results--no scarring and painless treatment. The Hilgartners (197) also had good results in treating not only trachoma but also pterygia maculae and opacities of the cornea. Over a period of 4 years, they have noticed no development of cataracts in any of their patients. They explain this on the basis of small dosages used over long periods of time.

Desjardins (27) after reviewing the great amount of literature on the subject, considers that roentgen rays have a "real and substantial effect on the lesions of trachoma." He states that this action is probably greatest during the early stages of the granular form of the disease.

For vernal conjunctivitis, Gifford considers (198) radium definitely indicated. Quick (199) reports 40 cases out of 82 apparently cured, 32 were definitely improved and 10 not improved. Lane (196) compiled 90 cases and considers radium almost a specific for this condition.

Roentgenotherapy is especially useful in blepharitis of the severe type which has proven refractory to other methods of treatment. Two or three X-ray treatments will often entirely relieve a condition of long-standing. Gifford (198) advises 1/5 to 1/2 epilation dose for this condition as well as for chronic dermatitis of the lids.

12. PEPTIC ULCER: In 1936, Schindler (200) reported a very interesting case of chronic hypertrophic ulcerative gastritis. This patient was observed over a period of 12 years during which time 65 gastroscopies were done. The diagnosis was made in 1922 by means of the gastroscope. There was continuous pain without improvement or relapse. In 1932, 45 X-ray treatments were administered according to the Coutard technic. Four weeks following treatment, normal gastric mucosa was demonstrated and this for

the first time since 1922. The patient was free of pain for the first time since 1918. In 1933, however, a definite atrophic gastritis developed with nervous symptoms predominating. On the basis of this case, he recommends this treatment in only the most severe cases of hypertrophic ulcerative gastritis which have been observed for some time and which fail to respond to usual methods of therapy.

Yugenberg (201) treated 365 cases of peptic ulcer; 203 were treated by local irradiation to the affected region and 159 were exposed to both local irradiation and radiation of the sixth to tenth thoracic segments of the spinal column. The latter method gave the best results. She reports complete recovery in 196 cases, marked improvement in 111 cases and failure of treatment in 42 cases. Then in 1936, Nemenow and Yugenberg (202) reported an additional series of 336 patients treated during 1934 and 1935. All had been treated previously by various methods; 49 had been operated and 133 were unable to work. The ulcers were in various locations: 41 of lesser curvature, 41 of the pyloric area, 133 of the duodenal cap, 25 of the jejunum after gastro-enterostomy and multiple ulcers in 66. In 25%, the symptoms disappeared shortly after irradiation; in 75% after initial improvement, there was an aggravation of symptoms which changed to improvement in many instances by the first month. Ulcers of the lesser

curvature showed the largest percentage of cures (60.9%) with 34.1% showing improvement, leaving 4.5% without results. Technic consisted of irradiation over an area including the stomach, duodenum and celiac ganglion; then over the spinal centers of the fifth to the twelfth thoracic segments. Single doses of 225 to 250 r. were given thru dorsal and ventral fields to the local region at intervals of 4 to 6 days, twice over each area. The spine was exposed to 250 r. thru a dorsal field, twice in 6 days. If recurrence, the entire series was repeated in 3 to 6 months.

13. BRONCHIECTASIS: Berck and Harris (203) treated 14 patients with bronchiectasis which was secondary to lung abscess. Seven were greatly improved, 2 moderately improved and 4 unimproved. There was one death after only partial treatment. They cross-fired the area involved thru anterior, lateral and posterior fields, giving 75 r. thru each field. The treatment was given 2 to 3 times a week for about 3 months. If the first course was inadequate, a second course was given after a period of 4 months. Desjardins (125) states that this report on bronchiectasis needs confirmation but it is nevertheless worthy of attention.

14. CARDIAC CONDITIONS: At least as early as 1916, reports were made of relief of cardiac pain by means of

roentgen rays. Aortitis has also been treated with relief of pain. Animal experiments indicate that the radiosensitiveness of the heart is relatively low and that it is able to tolerate doses well above the therapeutic range. (177)

Levy and Golden (204) have reported most of the work done in this country on cardiac conditions. In 1927, they reported having given a total of 139 radiations to 20 patients with rheumatic carditis, using doses of 1/10 E D. to the heart. Seventeen of these showed definite improvement. Eight cases showed mildly unpleasant symptoms for a time but in no case was there evidence of cardiac injury or unfavorable effects. The improvement noted consisted of cessation of fever, fall in heart rate, disappearance of leucocytosis and gain in weight. Changes in electrocardiograms on 14 cases were observed but these were evanescent and disappeared after a few days.

in 1928 (205) they reported 30 more cases with a total of 249 irradiations over the cardiac area. Unpleasant symptoms were noted in 14 cases but no evidence of unfavorable effect was observed. Twenty-one of the group showed clinical improvement at the end of the follow-up period. Five out of 7 with paroxysms of severe heart pain received relief. In 4 cases of sub-acute bacterial endocarditis there were no results. Three cases improved

temporarily, one was unimproved and 5 died. These 5 were cases of progressive cardiac failure.

In 1933 (206) they reported 32 additional cases of of rheumatic carditis. Seventeen had improvement, in 6 the therapy was doubtful as to value, 2 were unimproved and 7 died (2 of subacute bacterial endocarditis and 5 of cardiac insufficiency). Of 8 patients with paroxysmal heart pain, 5 were completely relieved, 2 temporarily improved and one was not affected. In all their cases, they have found no evidence of injury or unfavorable influence on the course of the disease. Seven cases which they have followed for 5 years, had no recurrence of trouble.

Their technic consisted of 10% E D. thru out the heart region according to a depth-dose chart and applied over an anterior and posterior field thru 0.5 mm. cu. and 1.0 mm. al. This is repeated at intervals of 2 weeks until 4 exposures. A new series may be given after from 1 to 3 months.

Desjardins (177) states: "Roentgen irradiation has been shown to have definite therapeutic value in certain cases of angina pectoris and certain varieties of myocarditis and aoritis."

Sussman (10) in 1930 gave the results obtained in some 90 cases of angina pectoris treated by Arrillaga, Groedel, Barrien and others. He then reported 16 severe cases which

had been recommended for alcohol injection of ganglia. After 6 months, 4 had not returned for observation, 1 died, 5 showed moderate improvement and 6 were almost completely relieved. He used suberythema doses at 200 Kv. thru 0.5 mm. cu. 4 mm. al. and celluloid. Irradiating a 10 x 20 cm. field, he arranged it so the length would extend along the posterior surface of the dorsal vertebrae from the seventh cervical caudally. 800 r. in 3 divided doses at 1 to 2 day intervals was given and in some cases repeated after one month.

15. NEURITIS AND NEURALGIA: Carter (207) names trigeminal neuralgia as one of the conditions in which roentgen rays have an analgesic effect. Meszoly (208) in 1935 reported 95 cases of trigeminal neuralgia of which 91% were cured. He used 400 to 450 r. at 170 Kv thru 0.5 zn. repeated 3 times at intervals of 6 weeks. If there was no improvement after the first treatment, a dose of 240 to 300 r. was applied to the bifurcation of the painful nerve, at the time of the second and third treatments. The immediate effect noticed in these cases was hyperemia, edema and increased pain. Lapeyre (209) reported 12 patients with 8 cures and no recurrence. Three of the 12 were temporarily improved but recurred. After another series, these were cured. He used a smaller dosage of 150 to 200 r. given twice a week for a series of 5 to 6

exposures. The series was repeated in some cases after 3 to 4 weeks. The retro-maxillary area was irradiated with the head tilted at an angle of 45 degrees. A second field may be used perpendicular to the side of the face at the naso-~~genital~~ labial fold. The frontal and temporal fossa may be irradiated perpendicular to the sella turcica in case of frontal pain predominating.

In 67 cases of sciatica, Meszoly (208) was quite successful. He secured 42 cures with marked improvement in 18 cases, some improvement in 5 and no change in 2. He treated the lower lumbar and sacral regions and the origin of the sciatic nerve in two fields of 15 x 20 cm. with 400 to 500 r. per field. Using this dose at 140 Kv thru 0.5 mm. of zn., he irradiated twice a week at 6 week intervals. If no relief was obtained, a dose of 300 r. was applied to the popliteal space, calf and ankle on the second and third treatments.

Delherm and Nilus (210) in 1933, reported the use of spinal and peripheral irradiation in sciatica. In 297 cases which received only spinal irradiation, 55% were cured, 25% improved, 17% remained stationary and 3% were worse. In 56 cases which seemed to require peripheral radiation also, 35 were cured, 12 improved and 9 unimproved. They exposed two fields on each side of the spine, between the tenth dorsal and third sacral verte-

brae. Small repeated doses of 300 to 400 r. were administered until a total of 1200 to 1600 r. had been given over a period of 10 to 14 days. 5 to 8 mm. of al. was used for filtration. When results were not satisfactory, peripheral irradiation was given at the sacro-iliac articulation, sciatic notch, popliteal space and painful points along the course of the nerve.

C. DERMATOLOGICAL CONDITIONS

After treating 1800 patients and giving about 10,000 treatments, Lane (211) reported his general impressions in regard to treatment of skin diseases. Individual characteristics of the skin to be treated such as age, sex, coloration, texture, congestion, site and type of tissue, all have a bearing on the intensity of the treatment to be used. Previous treatments and surface applications may increase the sensitiveness of the skin. He suggests the exposure of 3 or 4 small areas of skin to different doses of X-ray in order to determine the safe limit for that particular skin.

MacKee (212) stated that iodine, tar, mercury, chrysarobin, etc. enhanced the action of X-rays.

Hasley (213) in 1938 stresses the importance of the use of filtered X-rays, in preference to the unfiltered. He considers that when following Coutard's technic of heavy filters and low amperage, "there is a better skin

recovery than when following divided erythema or sub-erythema doses without filters." He advises filtered rays in dosages of 1/8 to 1/4 E D. in treating the common dermatoses. "They can be repeated often, if the diseased condition warrants it, with less hazard to the integrity of the skin."

1. ACNE VULGARIS: Tobias (16) treated 134 cases of acne vulgaris with X-rays. Sixty-eight were cured after one course, 22 after two courses and 34 were improved but not cured due to uncontrolled secondary factors complicating the condition. He considers that there are only two agents that will cure acne--nature and roentgen rays. Nature allows unnecessary scarring so irradiation is the better method to secure permanent cure with a minimum of scarring. He names 7 contributing causes which should be controlled if present. They are: (1) Seborrhea of the scalp (2) Digestive disturbances (3) Constipation (4) Focal infection (5) Anemia (6) Endocrine factors and (7) Occupational irritants. The best response to irradiation is obtained in severe indurated cases with excessive oiliness, deep hypertrophic lesions and pustulations. He uses $4\frac{1}{2}$ E D. as a maximum dosage over a year's time for oily skins and a maximum of $2\frac{1}{2}$ E D. for dry skins.

Hazen (214) treated 170 cases using dietary measures, arsenic internally, etc. in conjunction with roentgen therapy.

He states that irradiation is the quickest and surest method of controlling this disease. Fisher (215) treated 118 cases of which number 70% responded to the first course of treatment. Improvement was noted after the fifth or sixth treatment. The Martins (14) concluded that "all types of acne vulgaris appear to improve under roentgen ray treatment provided the proper degree of skin reaction is obtained." Pohle (122) in 1930 states that X-ray may be combined with medical attention such as dietary measures, bowel regulation and local ointments of non-irritating character. He advises unfiltered radiation, avoiding skin erythema.

Fox (15) treated 191 cases with 111 cures. Forty-seven cases were very much improved; in 27 cases there was improvement but they were unable to finish the course of treatment. In 4 cases, there were relapses. Two cases were complete failures. Southard (180) reported 12 cases which were all cured. Feldman (216) treated 66 cases with 60 apparent cures. Four improved and one was unimproved. Five cases had a mild recurrence which cleared on further treatment. Higgins (217) treated 31 cases. Only 4 of these had indefinite results.

2. <u>TUBERCULIDES:</u> Hazen (214) reported 2 cases with good results. Pohle (122) states that either radium or X-ray may be used in this condition, but he thinks that

ultraviolet light therapy is more efficient.

According to MacKee and Ciparillo (124) the results obtained with X-ray depend somewhat on the type of eruption. Ulcerated and hypertrophic lesions gave best results for them. Flat lesions with imbedded nodules responded unsatisfactorily. They consider that in most cases, X-ray or radium should be combined with other therapeutic measures. In selected cases, the Grenz rays may be useful. "Daily irradiation of the entire body with ultraviolet is of very real value."

3. TINEA TONSURANS: Fisher (215) considers X-ray therapy to be the method of choice in this condition. He uses the Kienbock-Adamson method which consists of epilating doses to the scalp. Pohle (122) describes the same method and adds that when the hair begins to fall, additional local treatment is indicated. Hazen (214) treated 350 cases using the Kienbock method which he considers to be the quickest and surest method of permanent cure.

4. FAVUS: Gunnlaugur (118) reported 152 cases of favus of the scalp which were treated in much the same way as tinea tonsurans. Pohle (122) advises the removal of the crusts before irradiation.

5. FUNGI INFECTIONS: McCormick (119) treated several hundred cases of dermatophytosis without recurrences. Local applications of vaseline, carron oil or unguentine

were used. Boric acid solution was used for bathing. Stockings were changed once or twice a day. Shoes were changed every day or two. Dorne and White (219) had very good results treating superficial yeast-like fungi infections with Grenz rays. They reported 40 cases using 8 Kv, 6 ma at 3 inches distance for one minute at weekly intervals for a series of 4 treatments. Hyphomycetic infections showed very little improvement. In 1932 (220) they reported 22 more cases with similar results. They consider the rays at this voltage to be superior to the usual X-rays in superficial micotic infections. (221)

6. HERPES ZOSTER: Carter (207) treated several cases of herpes zoster with good results. Keichline (218) in 1934 treated 62 cases. The ages of the patients ranged from 5 to 82 years. All were relieved of symptoms. 90% required only one dose and none required over 3 doses.

7. ECZEMA: Thoroczkay (222) in 1935 reported 101 cases of eczema which were followed from 4 to 9 years. 34.4% were cured, 12.9% were unchanged, 2.9% were worse than at the time of treatment and 15.6% had other areas affected at this time. Hesse (223) warns that if recurrence occurs, the cause has not been removed.

Pohle (122) considers roentgen rays to be one of the best therapeutic agents. He uses fractional dosages especially for the acute types. Fisher (215) treated 140

cases. Seventy were freed of eruptions, 40 were clinically cured, 30 improved but did not return for further treatment and 10 showed no improvement. In 30 cases there were relapses. Feldman (216) treated 129 cases with 118 apparent cures and only 9 recurrences. He found that the dry infiltrated form responded best. Eichenlaub (224) treated 100 cases of various dermatoses of eczematoid variety including urticarial eczema. He had only 4% failures.

Lane (211) found that chronic eczema responded best. He states that all causative factors should be removed as far as possible and believes that greasy applications increase the liability to erythema from radiation. Desjardins (126) states that all phases of eczema "react promptly to appropriate irradiation."

8. LICHEN PLANUS: Concerning this condition, Desjardins (126) makes the statement that "the therapeutic value of roentgen rays is generally so great one wonders why it is not better known and used more extensively." Hazen (214) reported 9 cases of which 8 were markedly improved.

9. MISCELLANEOUS: Feldman (216) treated 8 cases of sycosis successfully by means of temporary epilation. Marin (225) considers three methods of treatment in sycosis.

I Without epilation using 1/4 erythema dose per sector. 8 to 12 treatments may be required.

II Temporary epilation in 4 sittings at 3-day intervals using 1/4 erythema dose each time. This may

repeated once or twice after 8 days if the falling hair has not been hastened.

III Permanent epilation. Temporary epilating dose is given as in II then in 6 weeks 1/2 erythema dose is given every 3 weeks during the next 4 to 5 months.

In mycosis fungoides, Fisher (215) believes that "X-ray offers the greatest aid in allaying the itching and checking the disease" especially in its early stages. Desjardins (126) remarks that in this condition, the outlook is usually hopeless but "roentgen rays may delay the progress of the disease and prolong life for months and perhaps years." In some cases, there have been permanent cures according to reports. Arrest of the disease has been obtained in many cases.

In the case of psoriasis many instances of alleviation of the condition have been reported. However, it is still essentially an incurable disease because no method has been successful in preventing the recurrence of the lesions. Roentgen rays are often very effective in checking the exacerbations and in bringing about involution of the lesions especially if administered in fractional dosages. It must also be remembered that the lesions are extremely sensitive to the rays. (126)

DOSAGES USED BY VARIOUS RADIOLOGISTS
IN
ACUTE INFLAMMATIONS

| Condition | Reference | Remarks | Kvp. | Cu. mm. | Al. mm. | TSD cm. | Ma. | Min. | % ED. | Doses r. | Intervals Days | No. of Doses |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Carbuncles & Furuncles | (138) | | 85 | -- | -- | 25 | | | | 100-125 | 7 | 2-3 |
| Parotitis | (138) | | 125 | -- | 4-6 | 25 | | | | 125 | | 3-5 |
| | (134) | | 200 | 0.5 | 1 | 50-60 | | | ½ | 300 | | |
| Erysipelas & Cellulitis | (138) | Irradiate beyond margin | 85 | -- | -- | | | | | 125 | | |
| | (28) | | 120-140 | -- | 2-4 | | | | 33-50 | 200-350 | | |
| | (137) | | 100-130 | -- | 2 | | | | 25-33 | | 1 | 3 |
| Mastoiditis | (143) | | 100 | -- | 2 | 40 | 5 | 5 | 15-20 | 71.5 | | 1-3 |
| Cervical Adenitis | (146) | | 130 | -- | 6 | 40 | 5 | | 50 | 300 | 7-14 | |
| | (226) | | 125 | 0.25 | 1 | 25 | | | 10-20 | 80 | 3-5 | 1-5 |
| | (144) | | 150-180 | 0.5 | 3 | 30 | | | 20 | 260 | 5-7 | 2 |
| Gas Gangrene | (43) | Trunk | 130-160 | -- | -- | | | | | 100 | 1/2 | 6- |
| | | Extremity | 90-100 | -- | 1 | | | | | 100 | 1/2 | 6- |
| | (148) | | 88 | -- | 0.5 | 40 | 5 | 3 | | 45 | 1/2 | 8-10 |
| Puerperal Mastitis | (151) | | 172 | 0.5 | 1 | 30 | 4 | 3.5 | | 115 | 2 | 2-3 |
| | (150) | | | -- | -- | 4 | | | | 50-60 | | |
| Pneumonia | (152) | Diminishing Doses | 135 | -- | 3 | | | | | 250-350 | 1-2 | 3-4 |
| Lung Abscess | (155) | Ant. & Post. Fields | 150 | 0.5 | 1 | 30 | 3 | 3.5 | 20-25 | | | 1-5 |
| | (156) | Repeated in 4-5 weeks | 180 | 0.5 | 1 | | | | 25 | | 2-6 | 3-4 |

# DOSAGES USED BY VARIOUS RADIOLOGISTS IN CHRONIC INFLAMMATIONS

| Condition | References | Remarks | Kvp. | Cu. mm. | Al. mm. | TSD. cm. | Ma. | Min. | % ED. | Doses r. | Intervals Days | No. of Doses |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Sinusitis | (163) | Hypertrophic<br>Atrophic | 120<br>120 | --<br>-- | 4<br>4 | 27½<br>27½ | 5<br>5 | 10 | | 500<br>80 | 60<br>7 | <br>6 |
| | (164) | | 135 | -- | 4 | 30-35 | | | 37-50 | 150-200 | 14-21 | 3-5 |
| Actinomycosis | (28) | | | -- | -- | | | | 66-75 | 300-450 | 28 | |
| | (117) | | | 0.5 | 1.3 | 56 | | | | 240 | 1 | |
| Blastomycosis | (138) | | 125 | -- | 4-6 | 25 | | | | 500-600 | | |
| Pulmon. Tb. | (170) | | 178 | 0.5 Zn. | 0.5 | 30 | | | | 88 | 7 | 5-6 |
| | (8) | | | -- | -- | | | | 50-80 | | 28 | |
| Tb. Adenitis | (126) | | 130-140 | -- | -- | | | | 80 | | 30 | 3-12 |
| Tb.Peritonitis | (8) | Ant. & Post. Aspects | 130 | -- | 4-6 | | | | 60-80 | | 35 | |
| Tb. Iritis | (176) | | 120 | -- | -- | | | | 50 | | 4-7 | 3 |
| Tb.Genital Tract | (179) | Repeated after 6-9 wks. | 170-200 | 0.5 | -- | | | | | 35-100 | 7-21 | 3-4 |
| Unresolved Pneumonia | (24) | May be repeated in 10-14 da. | (125) | -- | 3 | | 5 | 5 | | | | |
| Gonorrheal Infections | (181) | Ant. & Post. alternately | 200 | 0.75 | 1 | 50 | 5 | 60 | | | 1 | |
| Arthritis Deformans | (57) | | 160 | 0.5 | 1 | 30-40 | Spine<br>Hip, Knee<br>Shoulder<br>Small Joints | | 180-200r<br>140-150r<br>120r<br>90-120r | | | |
| Arthritis | (186) | | | 0.5 | 1 | 30-40 | | | | 75-125 | 2 | 7-12 |
| | (12) | | 200 | 0.5 | 1 | | 30 | | | 80 | 3-4 | 4-6 |
| Bronchiectasis | (203) | 2 or 3 fields | 180-200 | 0.5 | 1 | 50 | 4 | | | 75 | 2-3 | |

# DERMATOLOGICAL INFLAMMATIONS

| Condition | Reference | Remarks | Kvp. | Cu. mm. | Al. mm. | TSD. cm. | Ma. | Min. | % ED. | Doses r. | Intervals Days | No. of Doses |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Acne Vulgaris | (16) | | | -- | -- | | | | 25 | | 7 | 14 |
| | (214) | Intervals increased 2/mo. | (125) | -- | -- | 22½ | 1 | 35sec | | | 3-4 | 5-8 |
| | (122) | | 80-100 | -- | -- | | | | | 30-100 | 4-14 | |
| Tuberculides | (214) | | (125) | -- | -- | 22½ | 4 | 1½ | | | | 1 |
| | (122) | | | | | | | | | 300-400 | | |
| Tinea Tonsurans | (214) | | (125) | -- | -- | 22½ | 4 | 85sec | | | | 1 |
| | (122) | | | -- | 1-2 | | | | | 300-400 | | |
| Favus | (118) | | 125-150 | -- | 0.5 | | | | | 350 | | |
| Dermatophytosis | (119) | Series repeated in 2-3 weeks | 85 | -- | 0.5 | 25 | 5 | 2-3 | | | 7-10 | 3 |
| | (221) | | 8-10 | -- | -- | 7½ | 6-12 | 1 | | 250 | | |
| Herpes Zoster | (218) | Treat local & Sp. root ganglia | | -- | 3 | 30 | | | | 148 | 10 | |
| Eczema | (126) | | 80 | -- | -- | | | | 10-20 | | 14 | |
| | (222) | | 110 | -- | 0.5 | | | | | 150-200 | | 1-4 |
| Lichen Planus | (126) | | | | | | | | | 75 | | 1-2 |

## VI CORRELATION OF X-RADIATION WITH OTHER THERAPY

When treating inflammations with X-ray or radium, one should not lose sight of the many other therapeutic measures which may serve to further shorten the course of the disease and lend comfort to the patient while in the healing process. The general condition of the patient is a very definite factor in his toleration of radiation as well as his response to it. Radiation has to be reduced in dosage and the series of treatments extended for individuals who are emaciated and generally run down.

### A. HEAT

The application of heat to tissues causes dilatation of the blood vessels, increasing circulation in the part and this way pressure in the immediate site of inflammation is somewhat relieved. Along with this effect, there is a soothing effect upon the sensory nerves which make the patient more comfortable. (227) The increased circulation allows a greater mobilization of leucocytes and more phagocytosis in the involved area. These results are considered beneficial in the therapy of inflammations. (228) It must be remembered that upon application of heat in case of a subsiding bacteremia, the vascular dilatation may cause the blood stream to again be flooded with organisms. There is also the tendency of heat to exaggerate the fluid exudation. If this exudation would inter-

fere with blood flow, the application of heat seems contra-indicated. Cold might actually provide more rapid flow of blood by decreasing the capillary pressure in this case. With this possible exception, there are no theoretical grounds for the use of cold applications in inflammations because the processes of immunity and phagocytosis are undoubtedly delayed as well as the circulation diminished. (228) Such results are antagonistic to X-ray therapy. Some authors consider the chief effect of X-ray in inflammations to be one of hyperemia. (34) (13) (74) (64)

Methods of heat application may be classified as: (a) Conduction - including the use of hot-water bottle, hot compress, hot bath and electric heating pad. (b) Convection - by means of the circulation of hot gases. (c) Radiation - including heliotherapy and therapeutic lamps of different types. Holmquest (229) after some experimentation considers tungsten and carbon filament lamps to be more efficient for the production of heat in tissues than infra-red generators using the same energy input. (d) Conversion - the use of electrical energy which is converted into heat within the body should also be considered. It includes the different forms of diathermy, radio thermy and electromagnetic induction.

Diathermy, of course, refers to heating the tissues with electricity. Electrodes are used so that the living

tissues become a part of the electrical circuit thru which high frequency currents pass. These range from 200,000 to 3,000,000 cycles per second. The direct effect of this passage of current is generation of heat within the tissue which is a part of the circuit.

Radiothermy may be considered a type of diathermy in which radio waves of very short wave length are produced and concentrated in the tissues by means of condenser plates. (230) The electromagnetic induction method makes use of alternating current of great frequency which sets up eddy currents in adjacent tissues or objects according to their relative conductivity. At present, this method seems to be the most nearly correct for the production of heat within tissues lying deep beneath the surface or for the production of fever. "The penetrating heat is produced at a greater rate in deep vascular tissue than in superficial fatty tissue. It is by far the most comfortable and least exhausting from the patients' point of view and it seems to satisfy all the requirements of safety and simplicity."(230)

The use of hot compresses and local hot applications is definitely indicated in carbuncles, furuncles and most pyogenic infection. Diathermy has been used effectively in pyogenic infections, pneumonia and sinusitis for example. Fever therapy is often a very effective measure in the arthritides, particularly gonorrheal arthritis. (232)

It is well to remember that hyperemic skin is more sensitive to X-radiation.

B. ULTRAVIOLET RAYS

Exposure to ultraviolet rays will produce erythema of the skin and if prolonged, severe burns may develop. They have a distinct bacteriocidal effect on the surface and deserve particular consideration when treating certain dermatological conditions. The susceptibility of skin to X-rays is increased by their use. (126) It is now known definitely that ultraviolet tanning of the skin does not increase the toleration for X-rays as was once thought. (124)

Lane (211) advises small doses of ultraviolet after the X-ray course in the treatment of acne. Desjardins (8) advises the use of daily ultraviolet baths over the entire body as well as X-ray therapy in tuberculosis of various organs. Mayer (174) is particularly impressed with the benefit derived from ultraviolet rays alone as well as in conjunction with X-rays, in tuberculous conditions. The rays have also been used in the treatment of erysipelas and varicose ulcers. (232)

C. SURFACE APPLICATIONS

These are particularly important in inflammations of the skin. MacKee (212) mentions iodine, tar, mercury, chrysarobin and salicylic acid as having their action enhanced by X-rays. Hazen (214) advises mild astringent

lotions in the treatment of certain cases of acne vulgaris. Lane (211) states that when sulfur ointment is used on skin lesions, more careful X-ray dosage is required because of the increased sensitivity. Mild antiseptics may be used in conjunction with radiation. Widmann (137) advised the use of boric acid compresses to the irradiated areas in erysipelas. He also stated that the eyes may be irrigated as required during the course of the disease. Kelly (43) used antiseptics as indicated in his gas gangrene cases.

D. SURGERY

In all inflammations under treatment by X-rays, one must be on the look out for surgical indications and the appropriate procedure should be instituted.

Carbuncles that are treated by X-ray require very little surgery if treated early. Lewis (44) advises daily dressings and any surgical treatment such as removal of slough, enlarging of sinuses or drilling of new sinuses which may be required. Irrigations with Dakin's solution may be used. Friedman (49) used stab incisions when suppuration had occurred as did Firor. (231)

Friedman (49) advises incision and drainage of abscess cavities when liquefaction and necrosis occurs in adenitis cases. Kelly (43) considers amputation to be a disadvantage in most gas gangrene cases. However, local surgical procedures should be used as needed.

In regard to tuberculosis of the female genital tract, Bickenbach (179) states that if ascites is present it should be tapped before radiation is begun. In case of laparotomy, radiation should be used after closure.

In actinomycosis and blastomycosis incision and drainage of pus cavities is an important part of the therapy. Radiation cannot take the place of surgery when it is indicated.

E. SERA AND BACTERIAL THERAPY

In cases of gas gangrene, Kelly (43) advises the use of tetanus anti-toxin (10,000 to 15,000 units) and gas gangrene anti-serum.

Anti-streptococcus serum may be used in erysipelas cases. It is usually given intramuscularly to avoid excessive reaction.

In a pneumonia which is on a pneumococcic basis, the type should be determined and the corresponding anti-pneumococcic serum should be given. 90 to 100 cc. of serum may be given intravenously. (227)

Autogenous vaccines may be employed in acne with success in certain cases. (16)

Non-specific protein therapy may be used very profitably in conditions such as arthritis, gonococcic infections and certain skin diseases.

Bacteriophage has been used with some success in

staphylococcic infections.

Transfusions may be used in anemias for example or in any of the usual indications. (227)

F. MEDICATION

1. DRUGS OF SPECIFIC ACTION

In actinomycosis and blastomycosis, potassium iodide has a definite action and should be used. In such cases, Stewart-Harrison (117) advises 4 to 6 grams per day along with X-radiation. Smith (165) and Dyes (116) also advise the use of K.I. It has been used in asthma, bronchitis, and chronic rheumatism as well. Other mycotic infections may respond to its use.

Salicylates are of great value in articular rheumatism before the pain is alleviated by X-radiation. It is possible to give as much as 8 grams a day in acute cases. The administration of salicylates with sodium bicarbonate often prevents gastric upsets. (227)

Sulfanilamide has proved to be practically a specific for the B. hemolytic streptococcus and should not be neglected in infections due to that organism. It has also been used in sepsis, gonorrhea, erysipelas, puerperal sepsis, streptococcic tonsillitis, meningococcic and staphylococcis infections. The maximum dose recommended is one gram per 20 pounds body weight per day. (233) Bohlman (234) reports remarkable results by the use of

sulfanilamide in 3 cases of gas gangrene. He used dosages of from 15 to 25 grains every 4 hours for 4 to 5 days. Dr. Hunt (121) on the basis of his clinical experience of using both sulfanilamide and X-ray, states that he is quite sure there is a ~~synergistic~~ supplementary action between the two.

Arsenic may be used for certain skin inflammations. Hazen (214) advises its use internally in acne vulgaris. Antuitrin S. may be of value in certain cases.

Digitalis has its special indications in heart conditions and should be used whenever such conditions begin to complicate the clinical "picture." For example, in pneumonia, beginning cardiac decompensation would be an indication for digitalis therapy. Heart stimulants may be required in certain cases. Oxygen treatment may also be of value. (152)

In anemic conditions, iron and liver therapy should be instituted according to the type of anemia to be treated. It should be remembered that anemia is not a contra-indication for X-ray therapy of inflammations. (89) but may be a factor in the poor general condition of the patient which makes him less tolerant of radiation. The value of radiation and ease of treatment in such cases may be greatly increased by proper management of the debilitating condition.

Ephedrine and epinephrine have a definite place in the treatment of sinusitis, asthma, rhinitis, etc. (227)

Antiseptics should be used as needed. Lazarus (178) in stubborn cases of ulcerative tuberculosis of the bladder advises methylene blue to be given in one grain, enteric coated capsules, 3 times a day. Then a bladder instillation of 2% sodium bicarbonate is given and held for ten minutes. It is washed out with warm sterile water and one ounce of methylene blue is injected and retained as long as possible. This is used in a course of 3 weeks followed by a course of oleum gomenal instillations.

2. PALLIATIVE DRUGS

The use of hypnotics, sedatives and analgesics may in some cases be an important part of the treatment of painful inflammations. Arthritis, neuritis, neuralgia, etc. may require them. In many cases during the first 12 to 24 hours following X-radiation, there is an exaggeration of pain and discomfort. (44) By means of the proper use of such drugs, the patient can be "tided" over this period of discomfort.

The value of morphine can hardly be over-estimated for the alleviation of pain in certain inflammations when irradiation is producing an exaggeration of symptoms. After this stage, sedation and analgesics may no longer be necessary because of the analgesic effects of the radiation. (227)

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