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X-ray therapy in acute peritonitis

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X-RAY THERAPY IN ACUTE PERITONITIS

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INTRODUCTION

It is the purpose of this paper first to evaluate the work done on the treatment of acute peritonitis with X-rays, and to attempt to reach some conclusion as to its value as a therapeutic agent in this disease; and secondly to review some of the outstanding theories and works on the mechanism of the action of X-rays on the human body, and from this review to arrive at a conclusion as to how these rays may have a beneficial effect in the treatment of acute peritonitis.

HISTORY

Of the marked advancements made in scientific medicine in the latter part of the nineteenth century none can surpass in significance and importance the almost accidental discovery of a new and hitherto unsuspected force made by Wilhelm Conrad Roentgen on the eighth of November in 1895 in the physical laboratory of the University of Wurzburg, according to Christie, (5). This force was described by Roentgen in his paper read before the Wurzburg Physico-Medical on December 8, 1895, as "A New Kind of Rays", (5). Christie describes this report as one which has rarely been surpassed in original reports as to completeness and accuracy.

Following this remarkable discovery physicists and doctors began to experiment with these new rays and to devise ways in which they might be aptly applied in medicine and surgery. The British Medical Journal as early as February 1896 devoted space each week to an article by Sidney Rowland entitled, "Report on the Application of the New Photography to Medicine and Surgery", (47). In one of Rowland's first reports he notes that a Professor Mosetig of Vienna was the first to operate "under the guidance of the exact knowledge of the anatomical structures obtained by the new radiation". Rowland

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(47), also notes that Professor Neusser was the first to apply the new discovery to medical diagnosis when the latter observed the shadows made on the plate by the stones in the patient's gallbladder. Since that time X-rays have come into wide use in the diagnosis of many other internal diseases.

The first suggestion of X-ray treatment of infections is seen early in 1896 when Sir Willoughby Wade, (51), in a letter to The British Medical Journal, suggests that since tubercle bacilli are destroyed by sunlight, it should be determined whether or not the new radiant has a sterilizing effect upon these bacilli. He suggests that these rays might be a means of sterilizing the tubercle bacilli within the body because of their obviously high penetrating power. These hopes of Wade's were soon dispelled, however, when a few weeks later Delepine, (10), stated that in his experiments comparing the growth, appearance, and virulence of various bacteria which had been exposed to X-rays, to those of the same strain which had not been so exposed, he was unable to detect any difference in the two groups. We know today that X-rays are bactericidal only if the bacteria are exposed to doses so great as to be far beyond human tolerance, and so the

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fact remains that it is useless to hope for direct bactericidal effect of X-rays in humans.

As early as 1896 it was known that these new rays were not without some danger. In that year King, (27), described severe burns suffered by a man who traveled around Canada demonstrating the phenomena of the new rays. In 1897 Walsh, (52), had observed several instances in X-ray workers in which there was evidence of deep tissue trauma resulting from X-ray exposure. Among these evidences are gastro-intestinal symptoms including nausea, vomiting and diarrhea.

In 1903 Murphy, (36), summarizes the therapeutic uses of X-rays up to that time which includes the treatment of granulomata of the spinal cord associated with vertebral tuberculosis, thereby relieving the paraplegia caused by this disease. In his textbook of the same year he mentions many skin diseases which have been treated successfully by X-ray therapy.

As mentioned above, the use of X-ray therapy dates back to 1896 and 1897 when these rays were not well understood nor easily controlled. Since the turn of the century, progress in the field of radiotherapy had been relatively slow up until the time of the First World War,

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but since that war the number of radiologists interested in the treatment of inflammatory conditions has steadily increased. Fried, (16), was one of the early workers in this field, and his reports did much to stimulate considerable subsequent interest in this type of therapy. It is only in the past few years, however, that X-ray has been reported as a therapeutic measure in the treatment of acute peritonitis. It appears at present that this method may never gain recognition and acceptance as a useful and popular therapeutic measure for this disease; largely, perhaps, because of the recent advent of the sulfonamide drugs and their wide acclaim and publicity, and their recommendation as a sure-fire cure in so many of the acute infectious conditions. Certainly these drugs are very dramatic in their successful results, but they are not successful in all conditions--they are by no means a panacea--and sight should not be lost of more valuable methods of treating certain conditions.

PRESENT CONCEPTS OF X-RAY THERAPY

The great majority of practicing physicians and surgeons have been very hesitant in accepting, much less trying, X-rays in the treatment of certain inflammatory conditions. Some of these men refuse to recognise even the slightest value of this method of treatment, and have put the idea of its possible usefulness far from their minds. Too many of these men because they cannot comprehend these mysterious rays are prone to stay entirely clear of them to such an extent as to ignore completely their therapeutic value except, perhaps, in the case of malignancies. Other men when thinking of X-rays, think only of their deleterious effects such as sometimes follow the injudicial or careless use of these rays, or as may follow the treatment of deep malignancies where the dosage, in some cases, is particularly high. It is true, that in the early days of X-ray there were many harmful effects associated with their use, but today with proper filtering and screening, accurate dosage control, the use of converging beams, and the better knowledge of human tolerance to them, it is possible to maximize the good effects and to minimize the ill effects of X-rays. It is also to be noted later that in the treatment of infectious conditions a low dosage is more beneficial

than is a large dose.

In defense of these skeptics, however, it is only fair to point out that many radiotherapeutists, like many other specialists, are very prone to favor their own field and ideas to such a degree as to lose their broad outlook on the particular problem at hand.

X-RAY THERAPY IN ACUTE PERITONITIS

The literature is remarkably barren on the subject of X-ray therapy in acute peritonitis. The clinical reports on such cases treated in this manner are especially rare; being limited, so far as I could discover in the English literature, only to the reports of Kelly and Dowell, (22, 24, 25). Pratt, (43), at Henry Ford Hospital has apparently used X-rays successfully as a prophylactic measure pre-operatively in fifty-one cases who subsequently had part of their colon resected. The experimental laboratory work related to this subject is somewhat more abundant, and seems to have been suggested by the clinical reports of the above mentioned men, for there is no experimental work of note on this subject prior to that time.

In 1925 Fried, (16), reported thesuccessful use of X-ray therapy in women suffering from various pelvic inflammatory diseases. In his series of fifty-two such cases forty-four had excellent or good results, while only eight had poor results. Of further significance is the fact that the patients receiving X-ray therapy spent thirteen percent less time in the hospital than did those who received medical or surgical treatment. A follow-up study of these patients revealed good re-

sults over a period of years. He does not intend that this treatment be used alone, but claims that its advantage lies in the fact that it hastens the localization of the inflammatory process and thus makes adequate drainage possible at an earlier date than do other therapeutic measures. The factors used by Fried in his X-ray treatment were as follows: Lilienfeld tube; 8 Ma., 100 to 140 Kvp., filter-- .5 mm. zinc plus .5 mm. aluminum, distance--25 to 50 cms. depending upon the condition treated. He never gave more than two irradiations to a patient. Although these cases were not those of acute peritonitis, they were similar enough so as to be applicable here.

In 1934 Kelly, (26), had his first opportunity to treat with X-rays a patient with general acute peritonitis. The case was that of a young girl who entered the hospital with the diagnosis of gangrenous appendix. The surgeon elected to operate at once, and upon opening the abdomen found a greatly distended gangrenous appendix and free fluid in the peritoneal cavity. On the following day a diagnosis of general peritonitis was made, and according to Kelly, (26), the attending physicians agreed that the case looked very bad and that Kelly could see what he could do with X-ray treatment, since the other

doctors had nothing to offer outside of general measures. Following the irradiation there was a prompt and favorable response, and the patient was dismissed from the hospital on the eighth postoperative day. From that time until the time that they published their book in 1942, Kelly and Dowell had treated fifty-one cases of general peritonitis following appendicitis. Some of these cases were irradiated postoperatively and others pre-operatively. The time relationship between irradiation and surgery depended on whether the surgeon elected to operate at once or to wait until after the more acute phase had subsided, hoping the inflammatory process would become localized. In either case, according to Kelly and Dowell, X-ray therapy is of definite benefit. In the pre-operative cases they claim that the toxic symptoms of the patient are rapidly decreased and that the localization of the inflammatory process is hastened. They state further, however, that the use of X-rays alone is not sufficient in those cases which have abscesses that must be drained or necrotic tissue that must be removed, and they do not suggest that this method of treatment replace medicine or surgery, but they do recommend that it be worked into the whole program of the treatment of such cases.

X-RAY THERAPY IN ACUTE PERITONITIS

The following table is taken from the book by Kelly and Dowell. It serves well to summarize their results and to compare them with the results of cases treated by other methods:

Table I.

Treatment of General Peritonitis after Appendicitis.

	No. Cases	Died	Mortality
General measures only	109	71	65.1 %
Sulfonamides and General Measures	42	16	38.0 %
Combination X-rays and Sulfonamides	21	7	33.3 %
X-rays and General Measures	30	6	20.0 %
TOTAL	202	100	49.5 %
Treated with X-rays	51	13	25.4 %
Treated without X-rays	151	87	57.6 %

Judging from the figures in this table, one cannot deny that they indicate that there is definite value in the treatment of general peritonitis with X-rays by the method used by Kelly and Dowell. It is also of interest to note that, according to these figures, X-rays without the coincidental use of the sulfonamides give better results than are obtained when they are used together. As to the morbidity, Kelly and Dowell state that those patients who have received the irradiations leave the hospital sooner

and in better condition than do those patients who have been treated otherwise. One may argue that this series of cases is not large enough to exclude the possibility of coincidence, and Kelly and Dowell admit this possibility in their publication at the time, but Kelly (25), states that since that publication he has continued to have the same good results up to the present time. Kelly and Dowell go so far as to advise, in their book, that any intra-abdominal condition which suggests a possibility of infection deserves immediate irradiation therapy to be continued until a diagnosis is made and other treatment instituted, or until the patient shows definite improvement, this within certain limits, of course. These men feel very optimistic as to the value of X-ray treatment of general peritonitis, as may be seen from the following quotation taken from their book:

> " We feel that the mortality rate can be reduced at least to ten percent or possibly more for appendicitis-peritonitis if X-ray treatment becomes more generally used in the early stage and sulfanilamide is not given simultaneously with X-rays."

As is true with other acute conditions, the earlier that the proper therapy is begun the sooner and better will be the results. As X-ray is so often left as the last resort in acute inflammatory conditions, the patient may

be all but lost by the time the radiotherapist gets to him; thus making it difficult for a fair conclusion to be reached regarding the value of this type of therapy.

The details of X-ray therapy employed by Kelly and Dowell depend upon the condition of the patient. They divide acute spreading peritonitis into five clinical stages as follows:

First stage: Appendicitis.
Second stage: Appendicitis plus localized peritonitis, which may go on to form a local abscess, or go on to stage three.
Third stage: Early spreading peritonitis, or the serosanguinous stage.
Fourth stage: The fibrinopurulent stage.
Fifth stage: Many adhesions and profuse collections of pus.

The constant technical factors are: 100 to 135 Kv., filter--1 to 5 mm. Al., or .25 mm. Cu. and 1 mm. Al., distance-- 40 cms., size of port--20 cm. by 30 cms. The variations of treatment for the different stages of peritonitis are only as to time and frequency of exposure and in dosage for the fifth stage. They are for the first and second stages 60 "r" to 80 "r" once per day for three days; for the third and fourth stages 60 "r" to 80 "r" two to three times per day for three to four days; for the fifth stage 50 "r" to 70 "r" twice daily for two to five days.

X-RAY THERAPY IN ACUTE PERITONITIS

Altemeier and Jones, (1), were among the first men to do laboratory experimentation on acute peritonitis. Their intention was to note what effect a large dose of X-rays would have in preventing death following a subsequent artificially induced acute peritonitis. This work was suggested to them by J. P. Pratt, who had noticed that in a series of fifty-one cases who were irradiated from six to eight weeks before resection of a portion of the colon, none developed a postoperative peritonitis, with one exception which was blamed upon an error in surgical technique.

The dosage of X-ray used by Altemeier and Jones in their experiments was very large for rabbits. They gave a single application of 630 "r" over the entire surface of the abdomen. The technical factors were 200 Kv., 25 Ma., filter-- .5 mm. Cu. and 1 mm. Al., distance -- 50 cms. Following this large dosage of X-ray, they noticed that there was a marked thickening of the abdominal wall and an increased volume of the peritoneal fluid which contained some red blood cells. Four weeks later the abdominal wall had resumed its original thickness and the peritoneal fluid volume had returned to normal as had its

cellular contants.

At varying intervals after irradiation, they injected into the peritoneal cavities of the rabbits 3 cc. of a brain broth mixture of the various types of organisms commonly found in a case of purulent peritonitis. All nonirradiated animals which were so treated died within twelve to fifteen hours after innoculation. The survival rate of the X-rayed animals varied considerably depending upon the time interval between irradiation and innoculation. They found that the greatest survival percentage was in the group innoculated five and one-half weeks after irradiation. In seventeen rabbits which were X-rayed between four and eight weeks previous to innoculation, twelve, or 70%, survived. In a similar control group all animals died. These experimental results showing the maximum survival rate to be between the fourth and seventh weeks after irradiation correspond closely with Pratt's work in which he obtained good clinical results when he irradiated his patients between four and six weeks prior to surgery.

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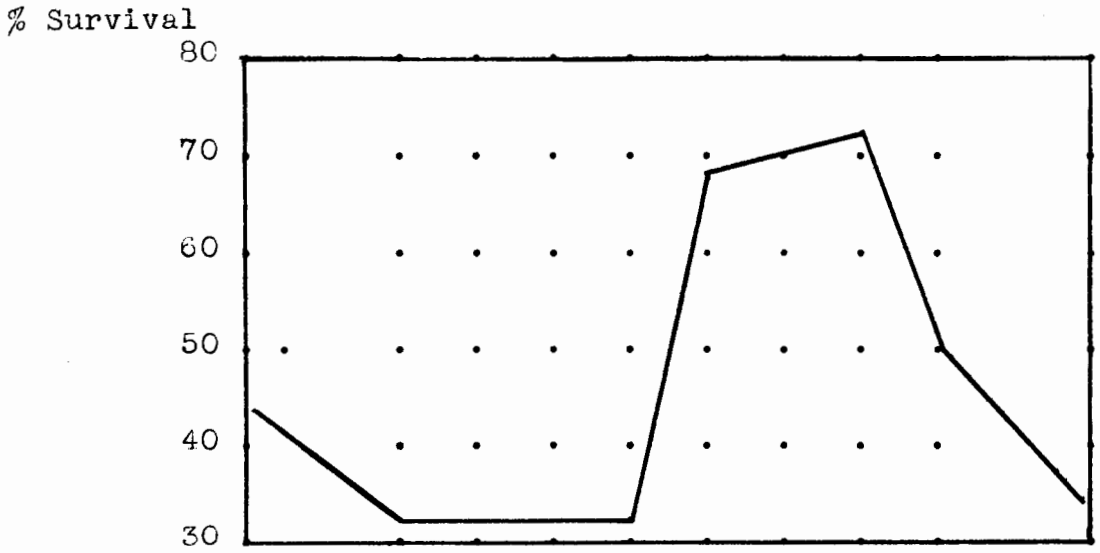
Table II.



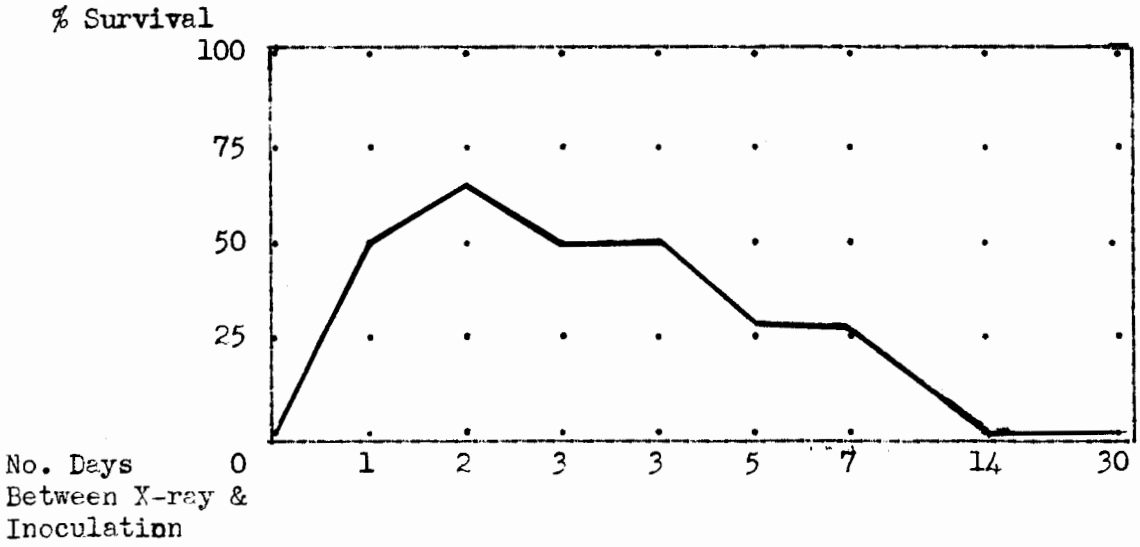
X-rayed--) Inoculation) Interval)	0-5 Hr.	24 Hr	72 Hr	1 Wk	2 Wk	3 Wk	4-4½ Wk	5-5½ Wk	6-7 Wk	4½ Mo.
No. Rabbits	7	3	3	3	3	3	7	8	2	3

Bisgard, Hunt, Neely and Scott, (2, 3, 4), had originally intended their experiments to compare the relative merits of the sulfonamides and X-rays in the treatment of acute artificially induced peritonitis, but as their work progressed, they noted several factors which caused them to alter their objective. Among these findings was the fact that the sulfa drugs did not have a very marked effect in decreasing the mortality rate in the experimental animals; also they noted that a relatively large number of the organisms--hemolytic Esher, coli-

was required to consistantly cause death in the rabbits. Both of these findings were indicative of the fact that they were dealing with a toxemia rather than with a frank infection. To further substantiate this belief, they used heat killed organisms of the same strain as previously mentioned, and discovered that the same mortality rate resulted. They had also intended to use a large dose of X-rays, but after irradiating several rabbits with 600 "r", they found that these animals developed a severe diarrhea and died within about a week's time. They then proceeded with their work using a dose of slightly more than 100 "r". By innoculating their animals at varying intervals after irradiation, they discovered that there was present in the X-rayed animals a protective quality which was not to be found in the non-irradiated control groups. In the latter groups there was consistantly a 100% mortality, while in the irradiated groups there was a varying survival rate depending upon the time interval between irradiation and innoculation. The greatest percentage of survival was found in that group which was irradiated forty-eight hours prior to innoculation. There was a degree of protection present after twenty-four hours, but of the animals innocu-

lated immediately after irradiation all died. Table III is a graphic summary of these results:

Table III.



Since the toxemia resulting from the heat killed hemolytic E. coli was due to an endotoxin, these men decided to see if the same protection would be induced in the animals by X-ray if an exotoxin was used. They used diphtheria toxin and obtained essentially the same results as they did when using the E. coli. They discovered further that this protective property must be present in the blood of these animals, since peritoneal washings or blood serum taken from animals forty-eight

hours after they were irradiated and then mixed with the organisms was capable of effecting a much higher survival rate in animals into which this admixture was injected than would similar admixtures of organisms and peritoneal fluid or serum from nonirradiated animals.

Though this work is not, as originally intended, a study of acute peritonitis in itself, it is certainly applicable here since the toxemia resulting from or associated with acute peritonitis is undoubtedly the cause of a major part of the clinical findings in this disease.

Bisgard is very cautious in his interpretation of his results, and mentions the possibility that other unknown mechanisms may be present and may be more or less responsible for the results here described. He says also, (3), that his main concern is not so much whether or not X-ray therapy may or may not be of value in the treatment of acute peritonitis, as it had been originally, but what is the nature of this protective mechanism which is apparently induced by X-rays.

Rigos at Mayo's, (46), experimented upon guinea pigs to determine if X-rays had a protective effect upon these animals after they had been innoculated with E. coli, and also to determine the effects of X-rays upon

the otherwise normal peritoneal fluid of the same species. In seven groups of four animals he gave two irradiations of 40 "r" to 50 "r" two hours after they had been innoculated with E. coli; out of the total twenty survived, 71.4%. In an equal number of animals that did not receive irradiation, but which were otherwise treated as the first group, sixteen survived, 57.1%. Obviously, this work cannot be valued so highly as those in which all controls died, and here also there is such a narrow margin between the survival percentages of the irradiated and the nonirradiated animals that the possibility of coincidence cannot be ignored. Continued repetition of these results would be necessary to establish the fact that X-rays were of value here. The X-ray factors used by Rigos were:

100 Kv., 5 Ma., filter--2 mm. Al., distance--51 cms., size of field--10 cms. by 7 cms.

Since his findings in the effects of X-rays on the cell counts of the peritoneal fluid are not significant here, they will be discussed in another part of this paper.

Rea, (44), did a group of experiments to determine the relative effects of various methods of treatment of acute peritonitis in rabbits. Among these methods is

X-ray therapy. He used only six controls and irradiated six other rabbits over the abdominal wall with 250 "r". The organisms used were those found in purulent peritonitis, and innoculated immediately before irradiation. From his results he concluded that X-ray had no place in the treatment of peritonitis because there was a higher survival rate among the controls than among the irradiated animals. Table IV summarizes his results:

Table IV.

	No. Animals	Live	Dead
Controls	6	2	4
Deep X-ray	6	1	5

It is pertinent here to discuss the various works presented above and to criticize them and to compare them where possible and to conclude from this just what value X-rays might have in the treatment or prevention of peritonitis. The works of these men are summarized in table V for convenience of comparison.

Table V.

		KELLY	BISGARD	ALTEMEIER	RIGOS	REA	CHROM
ANIMAL		Human	Rabbit	Rabbit	Guinea Pig	Rabbit	Mouse
ORGANISM		Intestinal Organisms (Pathologic)	Hemolyt. E. coli	Peritonitis Organisms (Mixture)	E. coli	Peritonitis Exudate	Spontaneous X-ray Deaths
AREA IRRADIATED		Abdomen	Abdomen	Abdomen	Abdomen	Abdomen	Whole Body | Abd. Only
X-RAY FACTORS	Kv.	100-130	140	200	100	250	160
	Filter	1 - 5 Al. or 1 Al.-.25 Cu	1 mm. Al - 5 mm. Cu	1 mm. Al. - 5 mm. Cu.	2 mm. Al.	1 mm. Al.	3 mm. Al. 5 mm. Cu.
	Ma.	---	15	25	5	---	4
	Dist.	40 cm.	50 cm.	50 cm.	51 cm.	60 cm.	42 cm.
TOTAL "r" DOSAGE		200 - 360	100 -	630	80 - 100	250	550 | 1100
(BEST) X-RAY INOCULATION INTERVAL		Variable	48 hrs.	5½ wks.	Inoculated 2 Hours Before X-ray	Inoculated Immediately After X-ray	-------
SURVIVAL %		80%	66.6%	70.0%	71.4%	16%	50-80% | 16%
SURVIVAL % OF CONTROLS		---	0.0%	0.0%	57.1%	33.3%	--- --

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On comparing merely the survival rates of these experiments, it would seem that there was little to be desired in establishing the value of X-rays in the treatment of peritonitis, but a more detailed examination of these works shows that there are many discrepancies in the results, the experimental techniques and the relative merits of the works and results. It would be well to consider each work separately in the light of the other experiments. Some repetition of previously mentioned facts is unavoidable.

Kelly's results are impressive and encouraging from a clinical standpoint, but there is wide variation in the condition that he is treating in man, and to use controls is, of course, out of the question. Only continued repetition of his results in a much larger series of cases will finally establish his contentions, if they are able to be born out. His results may be said to be indicative of what might be expected in a larger series of cases, but it is hazardous to speculate beyond that.

Bisgard is working primarily with a toxemia which is, of course, closely allied to general peritonitis. He used a single strain of a comparatively low-virulence organism, and a relatively low dosage of X-rays.

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It is the author's privilege to have worked under Dr. Bisgard on some of these experiments, and he knows the results to have been accurately reported and the experiments to have been carefully controlled. The author is also likely to be prejudiced despite his resolution not to be. One can safely conclude from Bisgard's work that X-rays given to rabbits forty-eight hours previous to innoculation with hemolytic E. coli or with diphtheria toxin imparted to these animals some anti-toxic factor which was generally distributed throughout their bodies, resulting in a decreased mortality rate in these X-rayed animals.

Altemeier demonstrated protective properties in rabbits, maximal at five and one-half weeks after irradiation, which time interval is not compatible with that found by Bisgard. It must be noted, however, that Altemeier used a much greater dose of X-rays, which Bisgard found to be lethal in his animals, and he also used a mixture of organisms to induce his experimental peritonitis, whereas Bisgard used only a single strain. Outside of these factors, their works are remarkably similar as to technique, etc., even to a survival rate of within less than four percent and with a 100% mortality in their controls. Another fact to be noted here is that Altemeier's

results bear out very closely the suggestion of Pratt, who suggested the experiment to him and who had prophylactically irradiated his patients four to six weeks preoperatively with very good results. It must be considered from this that the results were what they expected or hoped for. In evaluating this work, little criticism can be made of it, and its inconsistancies with Bisgard's work might be explained by their differences in technique.

Rigos, although he obtained a high survival rate among his irradiated animals, also had a high survival rate among his controls, consequently his work cannot be valued highly in establishing the value of X-rays in the treatment of peritonitis due to E. coli. The high survival rate among his controls is probably due to the fact that he used an organism of low virulence and low toxicity. Bisgard also used E. coli, but his strain was hemolytic and caused a much greater toxic effect in the animal. It must also be noted that, contrary to the findings of Altemeier and Bisgard, Rigos elicited his small degree of protection by irradiating after innoculation. The results of Rigos can only be of value if they are shown to be consistent in many repetitions. For this discussion they must be considered as insignificant.

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Rea shows by his results that deep X-ray has no effect in treating peritonitis because the survival rate among his nonirradiated animals was higher than that among his irradiated animals. However, in evaluating his work, it must be pointed out that his irradiation-innoculation time interval was essentially zero, which according to Altemeier and Bisgard is ineffective in affording protection. Further, the difference between the survival rates in his experiment, although 50%, is actually only one animal; these results are not in sharp enough contrast to be beyond the possibility of coincidence. Rea used only six controls and six irradiated animals, which is too small a group to demonstrate any factual evidence.

The work of Chrom is mentioned here, in part as a matter of interest, and to demonstrate that a very large dose of X-ray, (1100 "r"), given locally over the abdomen did not cause a spontaneous death, whereas only half of that dosage given over the entire body did result in a high mortality. This serves to support the work of Altemeier, who, in contrast to Bisgard, did not cause a spontaneous death in his animals when irradiated over the abdomen with 630 "r".

In the light of the foregoing data it is

hazardous to make any definite statements regarding the value of X-ray therapy in peritonitis. The evidence is conflicting and in some cases is not convincing. From these reports the most that one could conclude would be the following points, and these with reservations pending further substantiation or contradiction by subsequent works:

1. Some protective factor or factors are elicited in the bodies of rabbits by the action of X-rays on these animals.

2. There is indicative evidence that a similar factor or factors are produced in humans subsequent to irradiation.

3. The acceptable data on this subject is exceedingly limited, and on a few points apparently contradictory.

POSSIBLE MECHANISM OF THE ACTION OF X-RAY IN ACUTE PERITONITIS.

Since the beginning of X-rays, many men have devoted considerable time and effort to the study of the effects of these rays on living cells, tissues and bodies as a whole. The findings and reports of these men are numerous and confusing. Their theories are very simple, very complex and far reaching. Many of these works do yield valuable information, while others are of little consequence; but despite these many works and the many theories, no one can say definitely today how X-rays effect the bodies of animals and man so as to increase their resistance to certain infectious or toxic diseases.

It is not intended here to answer the question of how X-rays act on the body to cause it to become more resistant to bacteria and toxins, but merely to offer a suggestion based on the outstanding works along these lines as to how these effects may be explained.

Direct Bactericidal Effect.

It was Sir Willoughby Wade, (51), in 1896 who first suggested the use of X-rays to kill bacteria in the body, and although it was but a few weeks later that Delepine, (10), showed that the direct action of X-rays upon bacteria was not noticable, if present, many men

since that time have carried on experiments to ascertain if X-rays could not be found to be directly bactericidal. A few of these men are mentioned below together with their contributions.

Wolfender and Ross in 1898, (56), experimented upon the effects of X-rays upon the growth and activity of bacillus prodigious. They found that the X-rayed cultures showed much more abundant growth than did the non-X-rayed cultures after an equal period of time. They then X-rayed the media before planting the cultures on them and found no differences in the amount of growth on the X-rayed and the non-X-rayed media. From this they concluded that the X-rays had a stimulating effect directly upon the bacteria.

Wyckoff, in 1930, (57), found that hard X-rays killed bacteria in proportion to the measured air ionization.

Mohler and Taylor experimented upon the bactericidal effect of varying doses and quantities of X-rays. In their very technical discussion of their experiment they arrive at essentially the same conclusions as did Wyckoff.

In 1941 Pendergrass and Hodes state that X-rays

POSSIBLE MECHANISM OF THE ACTION OF X-RAY IN ACUTE PERITONITIS.

in large quantities, (tens of thousands of "r"), are bactericidal; that soft X-ray destroys bacteria more so than does hard X-ray; and also that the bactericidal qualities of X-ray increase with the temperature. They say that inflammations in man could not be benefited in this manner without causing irrepairable damage. In 1942 these men, (42), cite H. G. Korb as showing experimentally that 22,000 "r" generated at high Kv. had no effect upon tubercle and colon bacilli. When generated at 50 Kv., however, these same bacteria were killed with relatively small doses. They concluded from this that low voltage X-rays are absorbed more easily than hard irradiation and that they cause more intense ionization and more protein breakdown. They state further that heat alone will cause a similar protein denaturation of less intensity.

From these works one may conclude that the evidence is confusing. X-rays may be directly bactericidal under certain conditions, but the mechanism of this action is that of protein denaturation which would also effect normal body tissues in the same manner. Thus, killing bacteria within the body by means of X-rays is not practicable and it is probably not this mechanism that causes

protection against bacterial effects in the bodies of man or animals, especially since Bisgard and Altemeier demonstrated that the maximum protective effect is elicited when irradiation precedes bacterial entry into the body.

Indirect Bactericidal and Antitoxic Effect.

The next logical course of investigation is to determine if the blood of X-rayed animals or men has a greater bactericidal or antitoxic action than does normal blood.

In 1923 Warren and Whipple, (54), cultured from heart's blood, liver, etc., bacteria which are common to the intestinal tract. This blood stream invasion, they stated, was not an overwhelming bacteremia, however. This finding would tend to disprove the idea that the blood is more bactericidal following irradiation, but the irradiation used by these men was of rather high dosage.

Colebrook and Eidenow, (8), found that irradiation of several species of animals, including man, with infrared and ultraviolet rays resulted in an increased bactericidal power of their serum.

Fried, (16), in 1925, found that the active

serum withdrawn from patients with pelvic inflammatory diseases before they were irradiated had an incomplete bactericidal effect against anthrax bacilli; while this same serum, inactivated, showed no bactericidal effect. After irradiation he found that the active serum had a complete bactericidal effect and the inactivated serum had considerable such power against anthrax bacilli. This same action was found when staphylococcus aureus was used instead of the anthrax bacillus. Fried noticed this increased postirradiation bactericidal power to be present in two-thirds of the cases studied. He also noted that the organisms in an infected area completely died out within forty-eight hours after irradiation.

In 1939 Macht, (29), studied the growth of lupinus albus in normal blood and in the blood of irradiated persons and found that the growth was more profuse in the normal blood, and he concluded from this that the X-rays caused the production of some phytotoxic principle in the body. The blood from the irradiated persons was taken from patients receiving irradiation for cancer, skin conditions, etc., and from X-ray workers and from animals. In all cases this factor which inhibited the growth of lupinus albus was found to be present. The

degree of toxicity of the blood varied with the dosage and the animal. The toxicity was not evident till a few hours after irradiation--he found it maximum at twenty-four hours, however, he did not try it at forty-eight hours--and persisted for two to three days. He irradiated various parts of the body and found the greatest toxicity to result from irradiation of the head and the female abdomen. He used 250 "r" in all cases.

As mentioned previously, Bisgard, (2, 3), found that the serum and peritoneal fluid from irradiated animals afforded antitoxic protection when injected into other animals along with hemolytic E. coli. He found this protection present at twenty-four hours and maximum at forty-eight hours after irradiation.

From these reports one can conclude that there is present in the blood of irradiated animals some factor or factors which inhibit the growth of some bacteria, and which neutralize or destroy toxins, and which may be bactericidal. This is an effective, indirect and harmful effect of X-ray on bacteria within the body, but it is apparently not harmful to the body if the X-rays are given in reasonable dosage.

It now remains to speculate as to the cause of

this antibacterial and antitoxic effect induced in the body by means of X-ray exposure. To do this it would be well to notice the demonstrable effects of X-rays on various body mechanisms and structures.

Injury and Intoxication of the Body.

X-ray in large doses is known to cause various injuries to the body. These injuries may be manifested by burns, toxic symptoms, etc. The source of the toxic products and the manner in which X-ray produces or activates them is a matter of considerable dispute. Many theories have been advanced, but proofs are scarce. Hall and Whipple, (17), have done experimental work on X-ray intoxication on dogs, and noted that the general constitutional reaction of these animals to a lethal dose of X-ray is remarkably uniform. It was at least twenty-four hours after irradiation before the first toxic symptoms appeared. Vomiting, diarrhea, and increased urinary nitrogen dominate the picture until death on the fourth day. Autopsy of these dogs shows a small, fibrosed spleen; moderate mottling and congestion of the intestinal mucosa, and strong evidence of injury to the intestinal mucosa. The epithelium lining the intestinal

crypts may show actual necrosis. These men blame this general toxemia associated with vomiting and diarrhea onto the injury to the intestinal mucosal epithelium. Since they found that chloroform injury with associated liver necrosis did not modify the reaction of the dog to large or small doses of X-ray, they believed that the liver cells were not involved in the fatal X-ray intoxication.

Warren and Whipple, (53), in their work found that a unit dose of X-ray over the thorax caused no intoxication; whereas the same dose over the abdomen was lethal. This is contradictory to the findings of Chrom, (6), who found that 1,100 "r" over the abdomen was 16% fatal; whereas 550 "r" over the entire body was 50% to 80% fatal. Warren and Whipple believed that the systemic infection and intoxication is secondary to injury of the epithelium lining the small intestine. According to them this epithelium was injured before the lymphatic tissue was injured, and concluded that the former was more sensitive to X-ray. They also present evidence to verify the findings of Hall and Whipple, (17). Warren and Whipple in a subsequent work, (54), demonstrated intestinal bacteria in the blood stream, following irradiation, of laboratory animals. They believed that the

intestinal epithelium injury is the primary cause of this bacteremia. Mattrom and Kingsbury, (32), bear out this belief and support it with the results obtained from their experiments. They gave mice sufficient irradiation to cause a thrombopoenia and noted subsequently the presence of intestinal bacteria in the blood. They state that this bacteremia is due to leakage from the intestine made possible by X-ray injury to the intestinal epithelium.

Mulligan, (35), in 1942, reviews previous reports on autopsies following death closely associated with heavy X-ray therapy and finds in all cases severe damage to the gastro-intestinal tract with destruction of the epithelium of the intestinal mucosa.

Cori, (9), shows that the intestinal epithelium of mice is three times as sensitive to X-ray as is the skin of mice; and that the human intestine can bear without injury 130% of the erythematous dose of X-ray for man.

As to the injurious effects of X-ray, there seems to be no doubt of the damaging effect of heavy irradiation upon the intestinal mucosa. These injuries, of course, follow the use of much heavier doses than those recommended for the treatment or prevention of

peritonitis. The fact must be considered, however, that smaller doses of X-ray give rise to the antitoxic and antibactericidal factors in the blood. These smaller doses might also cause injury to the intestinal mucosa to a lesser degree than do the larger doses, and with this lesser injury there might be liberated into the blood stream a lesser number of intestinal bacteria which would act as antigens to give rise to a subsequent increased immunity against similar organisms, and to enhance the general bodily defense mechanisms for a short period of time. In the light of this, it would be of interest to look into the effects of X-ray on antibodies.

Effect on Antibodies.

Studies on the effect of X-ray on the formation and fate of antibodies have been made by many men. Simonds and Jones, (48), X-rayed rabbits ten to fifteen minutes each day for three weeks and then injected an antigen. They found that the agglutination titre was always higher on the controls than on the irradiated animals. Their study of opsonins revealed little, if any, difference between the controls and the irradiated animals. The compliment fixation reaction was not influenced by

X-rays; and their study of bacteriolysins was unsatisfactory.

Mattrom and Kingsbury, (32), found that sufficient irradiation to cause thrombopoenia and bacteremia resulting from intestinal injury was not sufficient to interfere with the general resistance of the animal to bacterial invasion, or with the production or presence of antibodies in the blood.

Hektoen, (20), using dogs and rabbits, found that irradiation with 37½ to 75 Kienbock units, (one unit is 1/10 erythema dose), at about the same time as antigen injection caused restraint in high degree, and in some conditions completely, of the production of antibodies as measured by the antibody content of the serum. However, when antibody production was at or near its height, in nonirradiated animals, X-ray had little or no effect on the antibodies in the blood. They also found that the spleen, lymphatic tissue and bone marrow were injured most by X-ray of this dosage, and concluded from this that these are the sites of antibody production, since their injury by X-ray is associated with suppression of antibody formation.

Hartley, (18), found that animals which had

been radiated with various rays, ultraviolet, infrared, and Roentgen rays, subsequent to immunization to diphtheria and typhoid did not demonstrate an increased antitoxic power.

From these works one finds evidence that X-rays have no effect on antibody production; neither a stimulating effect on antibody production nor a depressing effect on antibody production. The obvious conclusion, then, is that either the effect is variable or multiple, or that the methods of experimentation used by these men differ in such ways as to cause different results. The most that one can say regarding the effect of X-ray on antibodies is that it is questionable, if present.

Effect on Reticulo-endothelial System, And on Blood and Tissue Cells.

Many men have reported on the effect of X-rays on the reticulo-endothelial system, and on blood and tissue cells. Taylor, et al, (49); Thomas, et al, (50); Murphy and Ellis, (37); Murphy and Strum (38); Nakahara, (40); and many others--Simonds & Jones, (48); Mattrom, (32); Manoukhin, (30); Colebrook, (8); Desjardin, (11, 12, 13, 14)--agree that following irradiation there results a primary drop in leukocyte count, and especially

in the lymphocyte count. Following this there is a secondary increase to above normal followed after a varying time--two to three weeks--to a return to normal. The polymorphonuclear cells return to normal quite some time before the lymphocyte count returns to normal. Murphy and Strum, (38), produced this same effect by using dry heat, a light bulb, and raising the environmental temperature of the animals to 55 to 65 degrees centigrade. Nakahara, (39, 40), in studying histologically the lymph nodes and the spleens of these same animals which had been subjected to dry heat found an increased number of mitotic figures in the germinal centers of these organs, which finding he interpreted as evidence of regeneration. In studying similar organs in animals which had been subjected to small doses of X-ray, he did not notice any evidence of regeneration but he did notice evidence of a stimulative action on these organs which was demonstrable almost immediately following X-ray exposure, being most pronounced in forty-eight hours and persisted for two weeks. He concluded that the lymphocytosis induced by X-ray is due to a primary stimulative effect upon the lymphoid tissues of the animals; while the lymphocytosis induced by means of a dry heat is the effect of the re-

generation following the destructive action on these organs by the heat.

Rigos studied the effects of X-rays of the cell counts of the normal peritoneal fluid of guinea pigs. He found that doses of less than 100 "r" over the abdomen had little effect on the total cell count of the peritoneal fluid, but did cause a relative increase of macrophages and lymphocytes. Doses of 100 "r" caused an increased total count, while doses of 200 "r" or more caused a decreased total count, but a relative increase of macrophages. Montgomery, (34), however, has noted that in normal laboratory animals the cell counts of the peritoneal fluid varies widely among a species and between species, and also varies considerably with age. This finding of wide variation of the normal peritoneal cell counts casts a small doubt on the value of Rigo's results.

Chrom, (6), has made an interesting study on the effect of irradiation of the reticulo-endothelial system with regard to the power of the blood to sterilize itself after injecting bacteria intravenously. In the non-irradiated animals that were so injected, he found that the blood became sterile within about twelve hours. If the whole body were irradiated and then the bacilli injected, the blood did not become sterile. However, if

the liver and spleen alone were shielded and the rest of the body irradiated and then the bacteria introduced into the circulation, the blood became sterile within about sixteen hours. In these experiments he used from 400 "r" to 800 "r". In a subsequent work, (7), Chrom was not able to show these same results when using doses of from 10 "r" to 75 "r". He found that when using these doses the blood did not become sterile any sooner or later than did the blood of the nonirradiated controls. He concluded from his works that the reticulo-endothelial system, especially the liver, plays a very important part in removing bacteria from the blood stream, and that small doses of X-ray are ineffective in causing reduction of bacterial counts made on heart's blood.

From these works one may conclude that the evidence indicates that following irradiation with X-rays or other rays or dry heat there is a primary decrease in the leukocyte count followed by a secondary leukocytosis, the lymphocytes being effected more than the other leukocytes. The cells of the peritoneal fluid demonstrate essentially the same response to irradiation. These changes in the leukocyte counts are probably due to the stimulation of the lymphoid tissues by X-rays, or to the

regeneration of these tissues following their mild injury by heat, or perhaps both mechanisms take effect. It seems safe to conclude also that the reticulo-endothelial system is of great importance in removing bacteria from the circulation and that this system is stimulated by small doses of X-ray, although this is disputed, and destroyed by large doses of X-ray.

Other Theories and Observations.

Manoukhin, (30), in 1921 reported the successful treatment of various infectious and toxic diseases by irradiating the spleen with relatively small doses of X-ray. He believed this success to be due to the release of anti-substances from leukocytes which were broken down by X-ray. This lysis, according to Manoukhin, was caused by a special soluble ferment, "leukocytolysin". Leukocytosis, on the other hand, he believed to be caused by another soluble ferment, "anti-leukocytolysis", whose properties are opposed to those of the former ferment. He believes that the leukocytolysin is produced in the spleen, and that by irradiating the spleen its production is stimulated resulting in an increased leukocytolysis and thus an increased liberation

of antisubstances which combat the bacteria and toxins invading the body. Colebrook, (8), believed also that the leukocytosis is responsible for the increased bactericidal power of the blood of rabbits following irradiation; the products of the damaged cells evoking this reaction. Desjardins, (11,12,13,14), also favors the leukocytolysis theory as explaining relief obtained in inflammatory conditions following the use of X-ray. He suggests that the lysis of the leukocytes causes the liberation of antisubstances, and also believes that the reticular tissues are stimulated by X-rays so as to cause these tissue cells to proliferate and thus to increase the phagocytic capacity of the body.

Rigdon and Curl, (45), experimented upon the concentration of a dye, trypan blue, in local areas of skins of rabbits following irradiation of these local areas with 2,000 "r" of X-ray. They noted that the dye was concentrated in these local areas only when it was injected intravenously immediately before, immediately after, or one hour after irradiation. At these times of concentration there is no sign of hyperemia or edema, and thus this concentration was probably not due to either increased local blood supply or local venous

stasis. Histologic changes were not evident in these areas until three hours after irradiation. They believed that these phenoma of dye concentration are best explained by an increased permeability of the cell membranes in the irradiated area. There are many factors evident in these results for which an explanation cannot be found. Pendergrass and Hodes, (41,42), believed that the protective actions of X-ray are due to local hyperemia of the irradiated areas. With this hyperemia, they stated, there is an influx of leukocytes and a rapid removal of toxins and cellular debris. They believed that the localized increased immunity is accompanied by an increase in general body immunity as well.

One might suspect that if X-rays are of value in combating inflammatory and toxic conditions in the body, the sulfonamide drugs would be a valuable adjuvant. This, however, has been shown not to be the case when sulfanilamide or sulfathiazol is used in combination with X-ray. Kelly and Dowell, (23), Marks (31), Flocks, et al (15), and Harvey, et al (19), have all noticed the apoarent antagonistic action of these two therapeutic agents when used together.

POSSIBLE MECHANISM OF THE ACTION OF X-RAY IN ACUTE PERITONITIS.

Summary

In trying to summarize the results and the theories presented in this chapter, one is impressed by the diversity of opinions of the workers, and by the apparent confusion which is encountered in comparing these results and theories. To conclude from these data just what is the exact mechanism of action of X-ray in enhancing the body's resistance to bacteria and toxins is impossible. The experimental works vary considerably as to techniques and results, making it very difficult to compare them. The following is merely the author's opinion of what may be the mechanism of action of X-rays in peritonitis in animals and perhaps in man. The opinion is purely speculative, and is based on the following points derived from the above works.

1. X-rays cannot be used as a direct bactericidal agent in animal or man.

2. Small or moderate doses of X-ray do have an indirect bactericidal and antitoxic effect in the body.

3. Small and moderate doses of X-ray cause a primary leukocytolysis followed by a secondary leukocytosis, the main effect being on the lymphocytes.

4. Associated with No. 3 is evidence of

stimulation of the germinal centers of the lymphoid tissues.

5. These effects may also be caused by dry heat, infrared rays or ultraviolet rays.

6. The antibodies or their production are but little, if at all, affected by X-ray.

7. Large doses of X-ray cause severe cellular and tissue damage, while smaller doses cause a milder insult to or a stimulation of the body.

In view of these facts it appears that moderate or small doses of X-ray act as an irritant to the body as a whole as well as locally. This irritant action causes a mild generalized inflammatory reaction; thus stimulating the defense mechanisms of the body and thereby increasing the resistance of the body to bacterial invasion and to intoxication.

X-ray is merely a convenient and effective manner of causing such an irritant effect, and several other methods such as radiation with other rays, foreign protein injections, etc., might be equally effective.

SUMMARY

Following an introduction and a brief history of the development of X-ray, and a presentation of the present concepts of X-ray as a therapeutic agent; an evaluation of the effects of X-ray in the treatment of peritonitis has been made based upon clinical and experimental evidence. Some of the outstanding works on the effects of X-ray on various body structures and body mechanisms, and some of the theories connected with these works have been presented from which the author has attempted to arrive at a logical conclusion as to the mechanism of the beneficial action of X-ray therapy in peritonitis.

CONCLUSIONS

1. Experimental and clinical evidence indicate that X-ray therapy, properly administered, is of value in the treatment of peritonitis.

2. X-ray acts upon the body as a general, non-specific irritant causing stimulation of the defense mechanisms of the body, and thus increasing the resistance of the body to injury by the bacteria and the toxins associated with peritonitis.

3. Much more work must be done on these problems before these conclusions can be verified or disproved.

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