ROENTGEN RAY INTOXICATION.

III. THE PATH OF A BEAM OF HARD RAYS IN THE LIVING ORGANISM.

BY S. L. WARREN, M.D., AND G. H. WHIPPLE, M.D.

(From The George Williams Hooper Foundation for Medical Research, University of California Medical School, San Francisco, and the School of Medicine and Dentistry, University of Rochester, Rochester, N.Y.)

PLATE 45.

(Received for publication, July 6, 1923.)

All roentgenologists are deeply interested in the problems which may be formulated in these few questions: Do the hard x-rays follow a straight and narrow path from the x-ray target through the tissues of the human body? Do these hard x-rays suffer from reflection or refraction and therefore influence tissues outside of this direct pathway? What factor is secondary radiation in the treatment of disease and does such secondary radiation exert a toxic effect on tissue cells or tumor cells outside of the direct pathway of the hard x-rays?

The experiments outlined below help to give an answer to the above questions. We may say that our experiments indicate that the hard x-rays which injure the epithelial cells of the intestine travel in straight lines through the host’s tissues with no evidence that these rays are deviated to injure tissues outside of the direct x-ray pathway. It is probable that the same rays are concerned in the destruction of cancer cells and that the same statement applies to the path of such x-rays through living tissues.

It is obvious that the x-rays which influence the photographic plate or the retina (fluoroscope) travel in straight lines from the target through the living tissues. These rays are limited sharply by lead or other impervious screens. The x-rays which injure superficial epithelium (hard and soft rays) are sharply limited by impervious screens.

Theoretically it is impossible to outline the track of a beam of radiation through the deeper living tissues. The following possibilities
are to be considered. (a) The x-rays may pass through the living tissues in a straight line with no deviation and with no diminution in strength except as they are absorbed by various cells (Duane (3)) or as they decrease in energy in proportion to the square of the distance from the target (Voltz (12)). (b) The x-rays may be in part dispersed by reflection and refraction on contact with the cells of the living body (Shearer (9); Rankin and Chambers (7); Wilsey (14); Rosa (8)). (c) The x-rays may give rise to secondary radiation which may be effective at some distance from the sources (Müller (6); Chaoul (2); Taekel and Sippel (11)) or only locally near the point of incidence (Lindemann (4); Barkla (1)). Shearer thinks that about one-fifth of the radiation is scattered sidewise in the tissues.

Lindemann (4) thinks the metallic ions, mercury, iron, calcium, etc., in the tissues give rise to secondary radiation, which affects sensitive cells. He cites the spleen, duodenum and large intestine, liver, and leucocytes. Red blood cells, bile capillaries, and liver cells, however, are not injured by quite large amounts of radiation, yet they contain or are near a large supply of metallic elements.

Müller (6) finds that the ionization power of alpha, beta, and gamma radiation decreases in the proportion of 10,000:100:1 respectively. By analogy the deep effects of gamma radiation are supposed to be enhanced one hundredfold by secondary beta-rays. Szilard (10), on the other hand, states that secondary rays have 530 times less energy than primary rays. What actually happens in cells sensitive to radiation as it passes through or is absorbed by them is a matter for conjecture as we are dealing with living organs rather than with the photographic plate.

Method.

This study is concerned chiefly with observations made upon dogs in which intestinal lesions were produced for the purpose of studying regeneration after exposure to radiation. Usually far more radiation was used than is necessary merely to destroy the epithelium. The lesions were studied at periods varying from 5 days (Dog 19-122) to 69 days (Dog 20-50) after exposure to radiation. No distinction is made between the relative states of regeneration in the “chronic lesions” but they are spoken of roughly as “denuded” or “pathological” sections or surfaces. The uninjured mucosa is designated as “normal.” Only a few characteristic experiments are reported.

The same equipment was used as in the other studies (Warren and Whipple (13)). A Coolidge tube of medium focus, set at a constant
skin-target distance of 25 cm., was run at an E.M.F. of 90 to 100 kilovolts and a current strength (filament) of 8 milliamperes; 2 mm. sheets of aluminum were used throughout to filter the radiation. The amount of radiation varies somewhat in the different experiments; 2 mm. of lead-foil placed upon the skin of the abdomen was used as a screen. The apertures in the lead screen varied in size in the different experiments, some being round while others were square or rectangular.

The plane of the face of the target was at a 45° angle with the horizontal plane of the surface of the screen so that radiation advancing along a line drawn from the focal spot to the center of the aperture was always perpendicular to the plane of the screen or the skin and usually also to the longitudinal axis of the body of the dog.

The dogs were killed under ether anesthesia at different periods after radiation and the viscera examined in the gross and microscopically. An attempt was made to reconstruct the path of the radiation by putting together the injured intestinal sections in the abdomen at autopsy. The results are remarkably constant and the lesions are striking both in the gross and microscopically.

EXPERIMENTAL OBSERVATIONS.

Experiment 1.—Dog 19-127. July 15, 1919. Lead-foil (2 mm.) over thorax and upper abdomen down to costal margin. Radiation 350 M.A.M. at 95 kilovolts spread diffusely over the lower abdomen.

Autopsy.—5 days later. On opening the abdomen the intestinal peritoneum was entirely negative in the upper abdomen. Below the level of the costal margin the peritoneum was injected and the intestinal walls were flabby. The distinction was sharply defined at this level. On opening the lumen of the small intestine the mucosa of the upper one-third of the duodenum and most of the jejunum was normal in appearance. The transition between the normal and the pathological sections corresponded to the transverse line at the level of the costal margin and was as sharp as if the lesion were “made by the naked cautery.” It was limited microscopically to approximately two low power fields. This included the “disturbed” slightly atrophic epithelium at the edge of the lesion for a distance of about one-half a low power field.

The distinct and rather abrupt transition between the normal and injured areas may be explained by the fact that the actual area

---

1 Radiation and autopsy by Dr. Irvine McQuarrie.
radiated did not cover more than the area of a 7 or 8 inch circle and there was very little chance for much blurring of the edges of the screened area. The amount of radiation expended over each area was enough to injure practically all of the intestinal epithelium directly beneath the target. This experiment illustrates the efficiency and accuracy with which a large part of the deep body tissues may be protected while another part is being exposed to intensive radiation.

Experiment 2.—Dog 20-11, small fat well developed mongrel, male; weight 16 pounds. August 22, 1919. Given 456 M.A.M. of radiation under an E.M.F. of 90 kilovolts with a current strength of 8 milliamperes over the abdomen in the upper left quadrant and midline through an aperture 6 by 8 cm. square. The lead screen was 2 mm. in thickness.

The usual symptoms of intoxication followed a few days later and then cleared up. The dog was killed with ether anesthesia on the 7th day after radiation.

Autopsy.—No abnormalities in any of the viscera except the small intestine. There were several of these lesions—one in the lower third of the duodenum, six in the jejunum, and two in the upper ileum. The edges of these pale denuded areas were clean-cut and slightly rounded and marked off from the pale velvety mucosa by a slight injection of the villi. The transition from the normal to the denuded surfaces took place in 2 to 4 mm. as in the other experiments. On longitudinal section the margins of these depressed areas were precipitous. Occasionally these areas of injury were not sharply demarcated in intestinal loops. It is probable that such areas are to be explained by a coil or loop of intestine which was situated at the margin of the cone of radiation and therefore incompletely exposed to the x-rays. Roughly over one-third of the intestine was occupied by these denuded areas. Microscopically the transition from normal to the depressed and denuded surfaces took place within the space covered by less than two low power microscopic fields.

These two experiments showed recently produced or acute lesions of the intestinal tract which were sharply limited at their edges and conformed in extent on reconstruction to the intestine which was beneath the aperture in the lead screen.

Experiment 3.—Dog 20-4. November 26, 1919. Normal, active, young mongrel, female; weight 27 pounds. The abdomen was screened by lead-foil 2 mm. in thickness. A circular aperture 7.5 cm. in diameter was cut in the lead screen so that its center was placed approximately 1 cm. below the umbilicus in the midline; 400 M.A.M. of radiation were expended over this area under an E.M.F. of 90 kilovolts. The animal developed the usual symptoms of intoxication and died 7 days later.
Autopsy.—Immediately after death. No abnormalities other than those in the small intestine. The greater part of the jejunum was in the center of the abdomen and interspersed with it were many coils of the ileum. The walls of the jejunum especially seemed thin and flabby and pouted out in little pockets. On opening up the small intestine the greater part of the duodenum except for a few small short patches in the middle section was pale, velvety, and normal. The jejunum except for a few rather short sections of pale velvety mucosa presented a dark red glassy surface suggesting absence of the mucosa. The ileum mucosa, on the other hand, was alternately pale and velvety for a few inches and then dark red and glassy for 1 to 3 inches. The edges of these denuded sections were sharply demarcated, the transition occurring in 2 to 3 mm. About one-half of the total length of the small intestine was denuded of mucosa in this experiment. Microscopically these sections showed a transition from normal to the denuded area practically within the width of one low power microscopic field.

The lesions could hardly have been more sharply differentiated by the naked cautery. The denuded areas of greater length than the diameter of the aperture in the lead screen can readily be explained as occurring in those coils of intestine lying well within the 3 inch circle and not extending straight across it as some of the others do. On reconstruction at autopsy these lesions corresponded to the cone of radiation extended down through the depths of the abdomen.

Experiment 4.—Dog 19-21, normal, active old mongrel, female; weight 34 pounds. September 4, 1919. The abdomen was screened by lead-foil 2 mm. in thickness. An aperture 5 cm. in diameter in the lead screen was fixed at the level of the umbilicus in the midline. This area was exposed to 450 m.A.M. of radiation at an E.M.F. of 90 kilovolts. The dog was sacrificed on the 12th day under ether anesthesia.

Autopsy.—The skin had not broken down in the radiated area. The viscera were entirely negative, except for short isolated coils of intestine in the middle of the abdomen roughly in or near the midline. These abnormal parts were thin walled. The peritoneum over them was slightly rough and injected. They were distributed as follows: one in the lower duodenum, three in the jejunum, and two in the ileum. All were approximately 5 cm. in length though the intestinal coils shortened up somewhat on being exposed to the air. On opening the intestinal lumen the mucosa was seen to be pale and velvety to the edge of these sections. The sections themselves were slightly depressed, with a whitish somewhat granular surface. The transition at the edge to the normal mucosa occurred in a few millimeters and was sharp and very distinct. About one-quarter of the total length of the small intestine presented this abnormal appearance.
This experiment indicates that even in subacute lesions the sharp demarcation remains a characteristic of the lesions produced by the beam of radiation penetrating the deeper structures. The lack of regeneration of the mucosa in such experiments suggests the familiar skin x-ray ulcer reaction.

Experiment 5.—Dog 20-56, setter, good condition, male; weight 35 pounds. Given 480 M.A.M. of radiation at 90 kilovolts. January 8, 1920. The filter was 1\% mm. of sheet aluminum. The aperture in 1 mm. lead-foil was 7.5 cm. square and was located over the stomach. Under the fluoroscope the stomach filled with barium more than filled this aperture.

Autopsy.—11 weeks later. There was a sharply demarcated area, denuded of epithelium, on the anterior wall of the stomach between the greater and lesser curvatures directly beneath and corresponding to the location of the skin burn, approximately 4.5 by 7.5 cm. square. The stomach wall contracted down on exposure to the air and after fixation so that we had a rather distorted picture of the lesion (Fig. 1). There were similar denuded areas in various loops of the small intestine. Microscopically the transition from the normal to the denuded areas took place within two low power microscopic fields in both the stomach and intestinal lesions.

Experiment 6.—Dog 20-50. The 5 cm. circular aperture in the lead screen was placed over the mid-abdomen. December 12, 1919. Given 480 M.A.M. radiation by the usual method.

Autopsy.—69 days later. There were seven sharply demarcated sections in the small intestine denuded of mucosa corresponding to the size of the aperture in the lead screen—none more than 5 cm. in length. The ulcer edges were sharp and the transition from the normal to the denuded surfaces of the intestinal wall took place under the microscope within two low power fields. On reconstruction these chronic lesions corresponded to a truncated cone in the abdomen with its upper surface equal in size and shape to the aperture in the lead screen.

DISCUSSION.

The skin burn, when present, and the sharply limited and circumscribed injuries to the intestinal mucosa beneath it suggest that the type of radiation capable of injuring intestinal epithelium travels out from the target along the radii of progressively enlarging spheres just as light waves travel out from a point source. It appears probable that that part of the radiation which is absorbed by each successive layer of tissues is not dispersed in all directions to act upon the same or other tissues at a distance but affects the sensitive cells, by which
it is absorbed, or such cells as may be sensitive to its stimulus as the radiation passes through them.

There has been considerable speculation as to the factors which make one cell sensitive to these hard x-rays and a neighboring cell totally inert or resistant. Metallic ions have been suggested and this is as good an example as any. Ferments were very popular a few years ago and at that time these intangible agents were held responsible for this inexplicable cell individuality in reaction to the x-ray. All these suggestions fail when we attempt to explain the known facts. Why does the x-ray injure one type of leucocyte and not another and not at all the nucleated or non-nucleated red cells? Why does the x-ray injure germinal cells but not spinal cord and ganglia and other highly differentiated cells? These questions could be multiplied but we always come back to individual peculiarity of the cell. One cell is different or similar in function and entirely different or similar in reaction to the x-ray. Even if we cannot give the correct explanation, it is of interest to the physiologist and physician to be familiar with these individual peculiarities of body cells in their reaction to the hard x-rays. The physician should be able to avoid dangerous therapeutic exposure.

The most convincing lesion was found in the first portion of the duodenum—compare Experiment 1—and this observation has been repeated many times in different experiments. The first part of the duodenum is fixed fairly securely in the deepest part of the dog's abdomen just under the costal margin. Any beam of hard x-rays which injures its mucosa must have passed through skin, muscle, peritoneum, and several coils of small intestine. Yet we observe in the duodenum a clean-cut edge marking the normal from the destroyed mucosa. It seems to us that this indicates that these hard x-rays travel in straight lines through these various living tissues and that the secondary radiation which presumably is formed has no power to injure these mucosal cells or other body cells.

Martin and Rogers (5) have recently published pictures of lesions of the intestinal tract which were sharply defined by the use of screens, but they do not discuss the probable significance of this condition.

Intestinal motility is related to certain observations in these experiments. We are familiar with peristaltic activity in the stomach,
duodenum, and colon without any considerable change in the position of these viscera. The average physician thinks of the small intestine as combining peristaltic activity with considerable change in position of its coils or loops. Our experiments would indicate that in spite of active peristalsis there is very little if any change in position of various coils of the ileum and jejunum. How else may we explain these clear-cut ulcers in the small intestine of dogs exposed to hard x-rays over periods of 2 to 4 hours? Some of these animals were given morphia before radiation and there was clinical evidence of increased peristaltic activity as is usually caused by morphia in dogs. Many dogs were radiated without morphia and the findings were identical. It was often necessary to continue the x-ray exposure over 2 to 4 hours, including the time necessary for cooling the tube. If these loops of small intestine developed any change in position associated with peristalsis we would confidently expect much blurring of the zones of injury or even a diffuse injury of the small intestine. On the contrary we find a series of clear-cut areas of injury in the small gut corresponding to the cone of radiation as limited by the lead screen. All evidence then is against there being any change in position of the loops of jejunum and ileum in spite of active peristalsis during the period of radiation (2 to 4 hours).

SUMMARY.

X-rays which injure intestinal epithelium (and presumably other body or tumor cells) travel in straight lines from the target through the living tissues, forming a cone or beam of rays as controlled by impervious screens.

It is probable that secondary radiation is formed, especially deep in the body tissues, but such radiation does no injury to intestinal epithelium outside of the cone or path of radiation.

Lesions in the stomach and intestine may be confidently predicted from a knowledge of the size and form of the cone or beam of x-rays given over the abdomen. These lesions even more than skin burns do not heal and may in fact go on after many weeks to perforation.

Even in the depths of the abdomen the duodenal lesions are as clean-cut as a peptic ulcer, indicating the lack of dispersion or scattering of the primary or secondary rays in passage through the living
tissues. Transition from normal to necrotic mucosa rarely occupies more than 2 to 3 mm. and often can be observed in a single low power microscopic field.

BIBLIOGRAPHY.


EXPLANATION OF PLATE 45.

Fig. 1. Stomach "ulcer"—77 days after receiving 480 m.A.M. of radiation—8 milliamperes at an E.M.F. of 90 kilovolts. The skin-target distance is 10 inches with a 1½ mm. aluminum filter. The body screen aperture is 7.5 cm. square. The ulcer is 4.5 by 7.5 cm. and is sharply punched out. The edges are rolled. The exposed muscle is brownish and granular and edematous. A well organized clot stands out from the upper corner. The skin burn is similar in size and shape. Fluoroscopy at 5 weeks demonstrated a defect on the ventral stomach wall.
Fig. 1.

(Warren and Whipple: Roentgen ray intoxication. III.)