THE INFLUENCE OF X-RAY LESIONS OF THE INTESTINAL MUCOSA ON ABSORPTION OF GLUCOSE AND OTHER SUGARS

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Warren and Whipple (1) exposed the abdomen of dogs to large doses of x-rays. Up to the 2nd day after radiation the animals appeared normal; on the 3rd day they became nauseated, refused food and developed an intensive diarrhea. Death generally occurred on the 4th day, preceded by extreme prostration. A histological study revealed that the mucosa of the small intestine from the pylorus to the ileocecal valve was more or less affected. Damage of the nuclei of the crypt cells could be detected a few hours after exposure to radiation. Cell injury was definite after 24 hours and after 48 hours a disintegration set in which coincided with the appearance of clinical symptoms. 72 hours after radiation the destruction was quite extensive and at the time of death practically the whole mucosa had sloughed away. A marked increase in nitrogen excretion in the urine (Hall and Whipple (2)) and a fall in the alkaline reserve of the blood (Denis and Martin (3)) were noted after radiation.

Radiation of the abdomen of laboratory animals other than dogs (cats, rabbits, rats and mice) produced the same effects (4). The onset of diarrhea and of other clinical symptoms was always preceded by a definite latent period during which the well-being of the animals was apparently not disturbed. In rats and mice this latent period was found to be 2 to 3 days. Cori (5) established the minimal lethal x-ray dose for abdominal radiation of the mouse; when more than three times the lethal dose was administered, the latent period was not appreciably shortened nor was the occurrence of death accelerated. The intestinal mucosa of mice proved to be about three times more sensitive to x-rays than the skin.

It has seemed of interest to investigate whether the lesions which can be demonstrated histologically during the period prior to clinical symptoms after x-raying, are accompanied by a disturbance in physiological activity. In order to test the function of the epithelial cells, the rate of absorption of glucose and other sugars was determined in rats 20 and 40 hours after applying a sublethal dose of x-rays over the entire abdomen. Another group of rats received the same dose of x-rays over the thorax and served as control.

EXPERIMENTAL

Rats in the postabsorptive state, weighing 140 to 165 gm., were radiated. They were tied on the back and the body was shielded with 2 mm. lead with the exception of the part to be radiated. A Victor machine with Snook rectification was

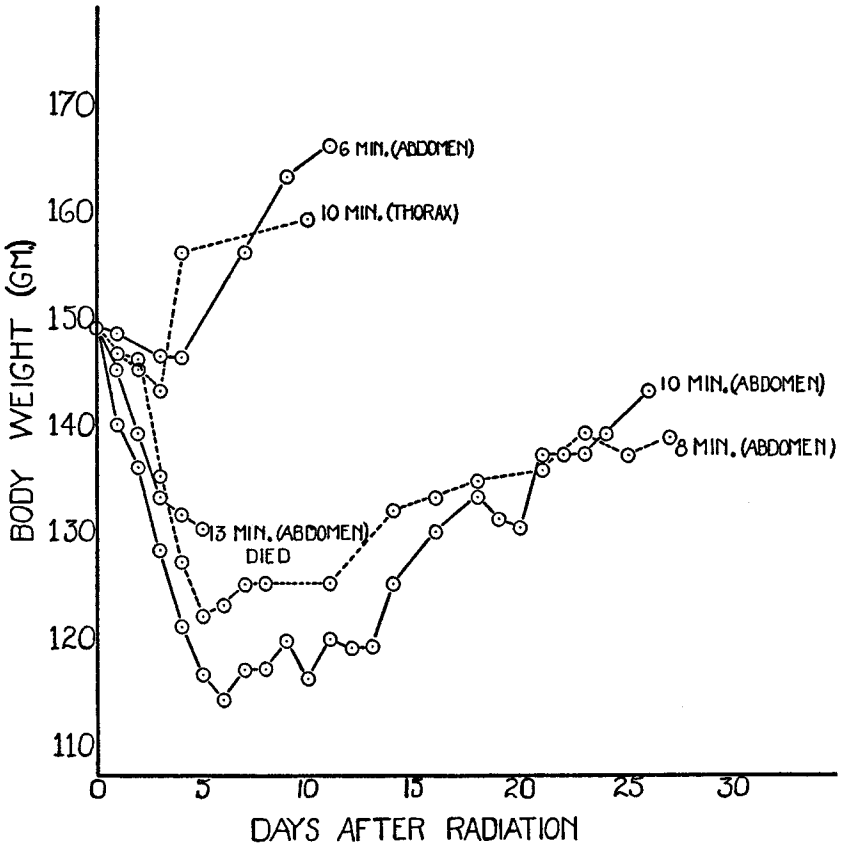

FIG. 1. Body weight of rats following radiation with different doses of x-rays. The conditions of radiation were as follows: 140 K.V.P. 5 ma. 25 cm. S.T.D. 2.5 mm. aluminum filter.

used, equipped with a stabilizer in the filament circuit, thus insuring a very constant x-ray output. An air-cooled Coolidge tube was operated at 5 ma. and 140 K.V.P. By actual ionization measurement the effective wave length of the radiation was 0.3 Å. The animals were placed at a distance of 25 cm. from the target and a filter of 2.5 mm. of aluminum was used.

As a preliminary step it was necessary to determine the lethal dose of x-rays for the standard conditions described above. A radiation of 16 minutes, applied over the entire abdomen, led to death on the 4th day, the animal having lost 21.5 per cent of its original body weight. Another rat receiving a radiation of 13 minutes duration died on the 5th day, the loss in body weight amounting to 12.7 per cent. Two rats which were given a radiation of 10 and 8 minutes survived, the greatest loss in body weight being 25.3 and 18.0 per cent respectively.

TABLE I

Absorption of 40 Per Cent Glucose Solution

20 hours after radiation and 24 hours after last feeding.

Thorax radiated			Glucose fed	Abdomen radiated		
Glucose absorbed per 100 gm. rat per hr.	Glucose absorbed in 2 hrs.	Body weight		Body weight	Glucose absorbed in 2 hrs.	Glucose absorbed per 100 gm. rat per hr.
mg.	*mg.*	*gm.*	*mg.*	*gm.*	*mg.*	*mg.*
184	583	158	895	158	460	145
194	603	155	915	165	422	128
250	772	154	900	154	633	204
224	760	169	915	168	539	163
167	580	173	930	160	372	116
204	590	144	910	149	560	187
222	640	144	860	143	635	220
Average..206 ±22	647	157	903	156	517	166 ±32

A radiation for 6 minutes caused a loss in body weight of only 0.2 per cent (Fig. 1).

In order to ascertain whether 10 minutes radiation was really a sublethal dose of x-rays, seven rats were radiated for this length of time. All of them survived, although they showed marked symptoms of x-ray intoxication. 2 or 3 days after radiation the animals became depressed and refused food. On the 4th day diarrhea developed and the body weight dropped markedly. Recovery set in on the 7th or 8th day and the animals slowly regained their original body weight. A composite weight curve for all the rats receiving 10 minutes radiation over the abdomen is shown in Fig. 1. In none of the radiated

rats was there any skin reaction or falling out of hair. As a control a rat was given a radiation of 10 minutes over the thorax; its body weight dropped only 0.4 per cent.

The rate of absorption of sugar from the intestine of rats treated with x-rays was determined by means of a method described previously (6). On each experimental day 2.4 cc. of the same sugar solution was fed by stomach tube to a rat radiated over the thorax and to one radiated over the abdomen. The two animals were of the same sex

TABLE II

Absorption of 40 Per Cent Glucose Solution

40 hours after radiation and 24 hours after last feeding.

Thorax radiated				Glucose fed	Abdomen radiated			
Glucose absorbed per 100 gm. rat per hr.	Glucose absorbed in 2 hrs.	Loss of original weight	Body weight		Body weight	Loss of original weight	Glucose absorbed in 2 hrs.	Glucose absorbed per 100 gm. rat per hr.
mg.	*mg.*	*per cent*	*gm.*	*mg.*	*gm.*	*per cent*	*mg.*	*mg.*
231	634	7.1	137	906	142	8.0	246	87
182	534	5.1	147	931	149	3.8	181	60
194	560	5.5	144	938	148	7.2	242	81
173	535	4.3	154	963	145	5.5	356	122
211	636	5.9	150	981	146	7.9	353	120
				905	157	6.0	242	77
				905	154	9.1	214	69
				905	157	11.0	238	72
Average..198 ±16	579	5.5	146	931 (924)*	151	7.3	259	86 ±18

* Average amount of glucose fed to rats radiated over thorax.

and of approximately the same weight. After 2 hours the rats were killed and the entire intestinal tract was analyzed for its sugar content, using Bertrand's method. The amount of sugar absorbed corresponded to the difference between the amount fed and that recovered from the intestinal tract. The glucose and fructose used were Pfanstiehl products, while the mannose was obtained from the Eastman Kodak Company.

Table I shows that 20 hours after x-ray treatment the rats radiated over the thorax had absorbed an average of 206 mg. of glucose, while

those radiated over the abdomen had absorbed only 166 mg. per 100 gm. rat per hour, a decrease of 19.4 per cent. 40 hours after radiation of the abdomen the average glucose absorption amounted to 86 mg. per 100 gm. rat per hour, a drop of 56.5 per cent when compared with the average absorption of 198 mg. per 100 gm. rat per hour of the con-

TABLE III

Absorption of 30 Per Cent Fructose Solution

40 hours after radiation and 24 hours after last feeding.

Thorax radiated				Sugar fed	Abdomen radiated			
Sugar absorbed per 100 gm. rat per hr.	Sugar absorbed in 2 hrs.	Loss of original weight	Body weight		Body weight	Loss of original weight	Sugar absorbed in 2 hrs.	Sugar absorbed per 100 gm. rat per hr.
mg.	*mg.*	*per cent*	*gm.*	*mg.*	*gm.*	*per cent*	*mg.*	*mg.*
77	223	3.0	144	600	148	2.6	144	48
97	303	5.7	156	660	161	4.1	197	61
73	224	5.6	152	660	141	6.3	137	48
Average..82	250	4.7	152	640	153	4.3	159	52

Absorption of 20 Per Cent Mannose Solution

40 hours after radiation and 24 hours after last feeding.

Thorax radiated				Sugar fed	Abdomen radiated			
Sugar absorbed per 100 gm. rat per hr.	Sugar absorbed in 2 hrs.	Loss of original weight	Body weight		Body weight	Loss of original weight	Sugar absorbed in 2 hrs.	Sugar absorbed per 100 gm. rat per hr.
mg.	*mg.*	*per cent*	*gm.*	*mg.*	*gm.*	*per cent*	*mg.*	*mg.*
20	60	4.9	145	460	142	6.5	20	7
27	86	4.9	154	423	150	4.1	30	10
27	63	6.2	135	440	140	3.9	40	13
Average..25	69	5.3	144	441	150	4.8	30	10

trol rats (Table II). In the last three experiments in Table II stomach and intestine were analyzed separately; the latter contained 8, 71 and 47 mg. of sugar respectively. If slow evacuation of the stomach were responsible for the diminished rate of absorption after radiation, the intestine should be free of sugar. Experiments at a later period than

40 hours after radiation could not be carried out because the sugar feeding was followed by diarrhea. Not only the rate of absorption of glucose but also that of fructose and mannose was markedly diminished following radiation of the abdomen (Table III). It may be assumed that this general impairment of the absorbing capacity of the intestine is a contributory factor to the intense diarrhea which develops at a later stage of x-ray intoxication.

The normal epithelial cells of the small intestine show a selective action on sugars, absorbing some more rapidly than others (6). It seemed of interest to investigate whether this selectivity was maintained after x-ray damage of the intestinal epithelium. The ratio in the rate of absorption of glucose, fructose and mannose in the control rats in Tables II and III was of the order 100:42:13. This is similar to the ratio of 100:43:19 obtained in a previous investigation (6). 40 hours after abdominal radiation the ratio in the rate of absorption of these three sugars was as 100:60:11. It may be concluded that the epithelial cells maintained their selective action on sugars.

Attention should be called to the fact that the average decrease in body weight in the first 40 hours after x-ray treatment was the same in the rats radiated over the thorax as in those radiated over the abdomen (Tables II and III) and that all animals appeared clinically normal at the time of sugar feeding.

Histological Findings

The author is indebted to Dr. K. Terplan of the Buffalo General Hospital for the following report.

Pieces of duodenum, jejunum and ileum were taken from rats killed 20 and 40 hours after radiation and from untreated rats. All animals had remained without food for 24 hours. The only macroscopically observable change was an increase in the amount of fluid in the intestinal lumen 40 hours after radiation. The microscopical findings were:

20 Hours after Radiation.—The chief pathological changes were to be noted in the crypt cells, consisting of various forms of degeneration of the nuclei. The latter were enlarged, took the stain poorly, the chromatin was granulated and resembled nucleoli. Other cells showed disintegration of the nuclear substance and formation of large vacuoles with inclusion of chromatin fragments. Some epithelial cells in which there occurred a marked mucin formation assumed the typical signet ring shape. Fragments of leucocytes were observed within a few

epithelial cells. There was a distinct diminution in the number of mitoses in the basal part of the intestinal glands. The whole gland structure was hazy. An increase in the number of leucocytes occurred in the stroma, some of them showing signs of disintegration. In the lymph follicles, especially those of the ileum, the lymphocytes showed marked nuclear disintegration and giant cells filled with nuclear fragments made their appearance.

40 Hours after Radiation.—The haziness of the structure and the number of leucocytes in the stroma were both increased. Mucin formation was even more marked than after 20 hours. There were again to be noted distinct signs of disintegration of the nuclei and invasion amongst the epithelial cells of leucocytes. More mitoses could be counted than after 20 hours but decidedly less than in the controls; there were also pathological mitoses with disintegration of the chromatin. The degenerative changes in the lymph follicles, which were so outspoken after 20 hours, had disappeared entirely. Summarizing it may be said that the early histological changes in the mucosa of the rat were very similar to those described by Warren and Whipple (1) in the dog, except that these authors did not mention the diminution in the number of mitoses and the disappearance of changes in the lymph follicles after 40 hours.

SUMMARY

A sublethal dose of x-rays was applied over the abdomen of rats and over the thorax for control purposes. 20 and 40 hours after radiation (*i.e.* during the "latent period") the rate of absorption of glucose, fructose and mannose was markedly diminished. Simultaneously definite histological changes were observed in the intestinal mucosa. In spite of the decrease in the absolute amount absorbed, the relative rate of absorption of the three sugars mentioned remained nearly unchanged, indicating that the epithelial cells retained their selective action on sugars.

The author wishes to take this opportunity to thank Dr. C. F. Cori for his helpful advice in carrying out this problem.

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