RADIATION-INDUCED GASTROINTESTINAL DEATH IN THE MONKEY

SCHOOL OF AVIATION MEDICINE
RANDOLPH AIR FORCE BASE, TEXAS

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This report describes the unique changes produced in the gastrointestinal tract of *Macaca mulatta* monkeys by supralethal doses of gamma radiation and discusses some of the inferences which may be made concerning the probable mechanism of the observed intestinal ulcers.

The classical concept of acute intestinal radiation death is based on the following hypothesis: Doses of ionizing radiation in excess of 1 kr suppress mitotic activity in the mucosa of the small intestine to such an extent that cell production cannot keep pace with cell desquamation (1). Ultimately, the mucosal surface is denuded of epithelium. In contrast the colon is relatively resistant to radiation. The loss of the epithelial barrier of the small intestine is thought to lead to death through the loss of large volumes of fluid and electrolytes via the gastrointestinal tract (1,2). Bacteria are said to play a minor role in this mode of radiation death (1,3,4,5).

In mice, rats, and dogs gut death is produced by doses of total-body x-radiation or gamma radiation of the magnitude of 1 to 10 kr. Death usually occurs within 3 to 5 days. Survival time is nearly invariant with increases in radiation dose above the level of 2 kr until the central nervous system (CNS) mode of death intervenes at about 10 kr (1,3,4,5).

There are numerous reports describing the natural sequence of cell maturation and migration in the intestinal epithelium. Radiation effects on this orderly cycle have been the subject of intense investigation (6,7,8). Some observations support the classical hypothesis of the mechanism of denudation. Indeed, the literature contains so much supportive evidence for the denudation theory that in some species the hypothesis has become a conclusion (1,2).

Little is known about the exact sequence of events in acute intestinal death in man. On the basis of the few cases available for study, it has been assumed that the sequence of events is probably the same as in the mouse and dog (2). Although this may be the case, in recent years a number of reports have suggested that a slightly different but vastly important train of events occurs in some animals (9,10). One such animal is the rhesus monkey *(Macaca mulatta)*, a primate that is biologically more similar to man than are rats, mice, and dogs.

In the rhesus monkey irradiated with 1.5 to 7.5 kr the most severe anatomic changes at death are in the gastrointestinal tract. The small intestine is not preferentially damaged. The colon is equally or perhaps more severely affected. Ulceration in stomach and colon is frequently observed. The survival time of 4 to 9 days is considerably longer than that of the aforementioned species (11).

MATERIALS AND METHODS

Ninety-nine monkeys were divided into groups of 5 to 8 animals each. The animals weighed from 5 to 7 pounds each and were clinically free of disease. Throughout the experiment the animals were maintained under conditions described earlier (11,12).

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This work was accomplished at the Radiobiological Laboratory of the University of Texas and the United States Air Force, Austin, Tex.

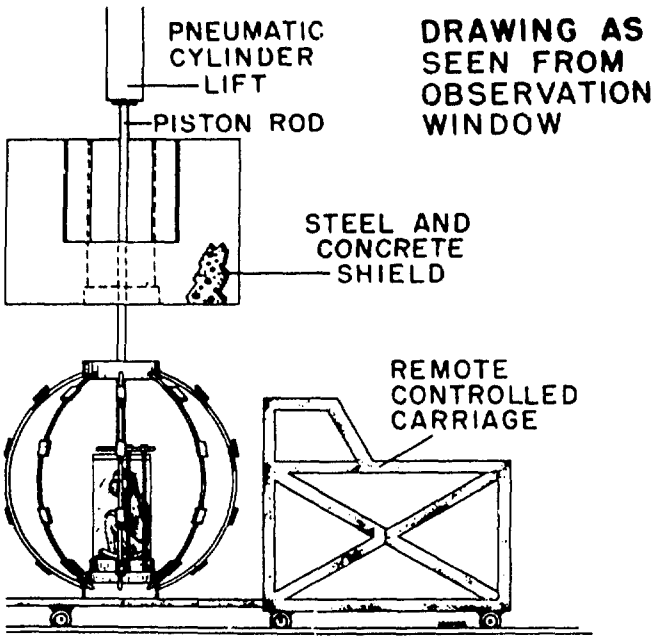

FIGURE 1

Each monkey was irradiated separately. The subject was retained within the shield until the carriage moved the sources into position and then was lowered rapidly into the center of the field. The dose rate was 803 r per minute.

Figure 1 diagrammatically depicts the radiation facility. Thirty-two cobalt-60 sources rated at 237 curies each were uniformly distributed over a spherical wire frame 26 inches in diameter. The dose rate at the center of the sphere was 803 r per minute. There was less than 5 percent variation in dose rate throughout the cylindric 8- by 15-inch plastic exposure chamber (11). Radiation doses ranged from 400 to 40,000 r.

The animals were fed and watered at 9 a.m. Each animal was irradiated separately and in sequence between 10:45 p.m. and 6:30 a.m. Following exposure they were kept in individual cages. Every animal was subjected to complete necropsy immediately after death. Two sets of tissue samples were obtained. One set was fixed in Bouin's solution, and the other was placed in neutral 10 percent phosphate-buffered formalin. The tissue was paraffin-sectioned and routinely stained with hematoxylin and eosin. Special stains were utilized when indicated.

A previous report presented the pathologic findings in the 20 subjects dying a CNS death (13). With two exceptions these were animals irradiated with 10 kr or more. One monkey that received 10 kr survived beyond the CNS phase of death; another receiving 5 kr died a CNS death. Both of these are excluded from the statistical data in this paper, but so far as the morbid anatomy is concerned, the 10 kr animal is considered an acute intestinal death. The remaining animals under consideration in this report were grouped as follows: 8 at 1.5 kr; 8 at 2.0 kr; 8 at 2.5 kr; 7 at 5.0 kr; and 5 at 7.5 kr.

All of the autopsy material was first examined without an exact knowledge of the radiation dose administered to each animal. The anatomic diagnoses and clinical diagnoses usually coincided (11). Another set of slides was assigned a set of code numbers, the key to which was known only by one technician. The histologic preparations examined in this fashion included the following: three sections of stomach — one from the fundus, one from the body, and one from the prepyloric region; three sections of small intestine — the duodenum, jejunum, and ileum, respectively; and three sections of the colon — one from the cecum, one from the sigmoid, and one from the rectum. All histologic interpretations were completed before the doses administered were revealed to the examiner.

RESULTS

The 45 monkeys receiving between 1.5 and 7.5 kr exhibited a relatively uniform physical reaction which has been discussed at length by Allen et al. (11). Following the initial episodes of vomiting, diarrhea, nystagmus, and tremors occurring during and immediately after irradiation, the animals rapidly recovered. By the 5th postirradiation day, however, anorexia and diarrhea became prominent. Once these signs developed in an animal they persisted until death. Emaciation and dehydration were prominent in all of the animals and became more severe the longer the animal survived. In some cases there was as much as a 30 to 35 percent weight loss by the time of death. The

first death occurred on the 4th day and the last on the 9th day. The single animal to die on the 4th day received 5 kr. On the 5th day, 2 animals exposed to 7.5 kr and 1 animal exposed to 5 kr died. On the 6th, 7th, and 8th days most of the remaining animals died, and there was indiscriminate mixing of dose groups with the exception of 8 animals given 1.5 kr. Four of these died on day 8 and 4 died on day 9. The daily distribution of deaths is illustrated in figure 2. The survival times of individual animals and groups of animals are depicted in figure 3.

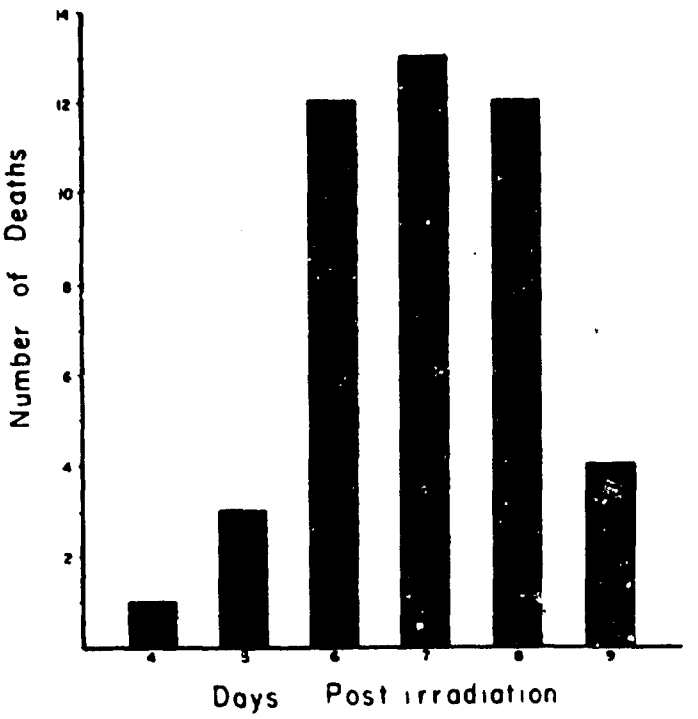

FIGURE 2.

The daily distribution of deaths. The animal dying on day 4 received 5 kr. Two 7.5 kr animals and a 5 kr animal died on day 5. On days 6, 7, and 8 there was indiscriminate mixing of dose groups except for the 1.5 kr animals. Four of these died on day 8 and 4 died on day 9.

Gastrointestinal lesions

The common denominator in the stomach, small intestine, and colon was mucosal atrophy. Although the histologic changes in the small intestine and colon were essentially the same, the incidence of ulceration in the two organs was strikingly different.

Stomach

In 14 animals the gastric mucosa was ulcerated. Typically such an affected area was covered by a light green fibrin membrane containing numerous colonies of bacteria (figs. 4 to 6). The mucosa was hemorrhagic, but only superficially eroded. There were occasional faint remnants of gastric glands widely separated by edematous, hemorrhagic lamina propria. Bacteria could be found invading the stomach wall, occasionally as far as the subserosal lymphatics. The hemorrhagic necrosis, however, was usually limited to the mucosa. The muscularis mucosa was generally intact. Immediately beneath the ulcerated area, the submucosae were severely edematous.

The repetitious pattern of gastric ulceration was striking. In each instance, ulceration occurred primarily in the body of the stomach. The fundal and prepyloric mucosae were relatively unaffected. Hence, when the stomach was opened along the greater curvature there was a tendency for the ulcerated areas to assume a butterfly configuration (fig. 5). It is notable that this is the portion of the mucosa richest in parietal cells.

The incidence of gastric ulceration increased strikingly as the total dose of radiation increased (fig. 7). Figure 8 shows the percentage occurrence of ulceration in the radiation dose groups as they were combined for statistical analysis by the chi-square test. It was necessary to combine adjacent dose groups since the chi-square test requires that for degrees of freedom larger than 1, fewer than 20 percent of the cells should have an expected frequency of less than 5, and no cell should have an expected frequency of less than 1 (14). The statistical analysis yielded a chi-square value of 9.008, which for 2 degrees of freedom is significant beyond the 2 percent confidence level and demonstrates that the frequency of ulceration increased significantly as a function of relative radiation dose.

The data in figure 3 suggested that there might be a correlation between gastric ulceration and survival time. In order to determine

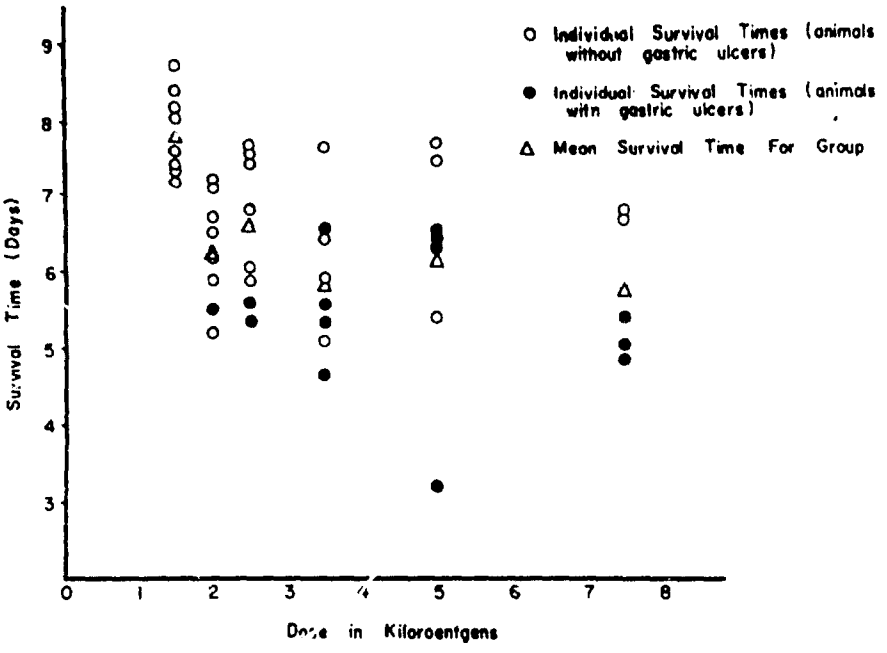

FIGURE 3

Survival time decreased only slightly with increasing dose, particularly in the dose range of 2.0 kr to 7.5 kr. The survival time of the 1.5 kr animals was significantly longer than the higher dose groups.

this relationship independently of dose, the partial correlation technic of Guilford was employed (15). This technic allows the correlation between two variables to be determined with the relation of a third variable to each ruled out. Accordingly, product-moment correlations were determined between dose and time to death, ulcers and time to death, and dose and ulcers. The point biserial correlation coefficient, a product-moment coefficient, for dose and ulcers was computed to be +.4706. This value is significant beyond the 1 percent confidence level, substantiating the positive relationship between dose and occurrence of ulceration. The product-moment correlation coefficient for dose and time to death was found to be −.5739 ($P = .01$) demonstrating that the higher the dose, the sooner the animals die. The point biserial correlation coefficient between ulcers and time to death was −.6862, giving a negative relationship between occurrence of ulceration and time to death. After ruling out the influence of dosage by using the partial correlation technic the correlation between ulcers and death was found to be −.576, a value which is still significant beyond the 1 percent confidence level. Hence animals with gastric ulcers died earlier than animals without gastric ulcers irrespective of dose (fig. 3). Extracting the relationship between ulcers and each of the variables dose and death, the correlation between dose and death was found to be .3909 ($P = .01$). There was a more significant relation between ulcers and time to death than between dose and time to death.

In 31 animals the gastric mucosa was grossly intact, but in 19 of these there were varying degrees of atrophic gastritis. Again, the gastric glands of the body of the stomach were the most severely affected (fig. 9). Occurrence of the more severe cases of mucosal atrophy was random with regard to survival time and dose. However, of the 12 animals that failed to develop atrophic gastritis, 5 received only 1.5 kr, 5 received only 2.0 kr, and there was 1 animal from each of the 3.5 and 7.5 kr groups.

FIGURE 4

Stomach of animal dying 5 days postirradiation with 7.5 kr. The hemorrhagic mucosa is covered by a thick, grayish-green fibrin membrane.

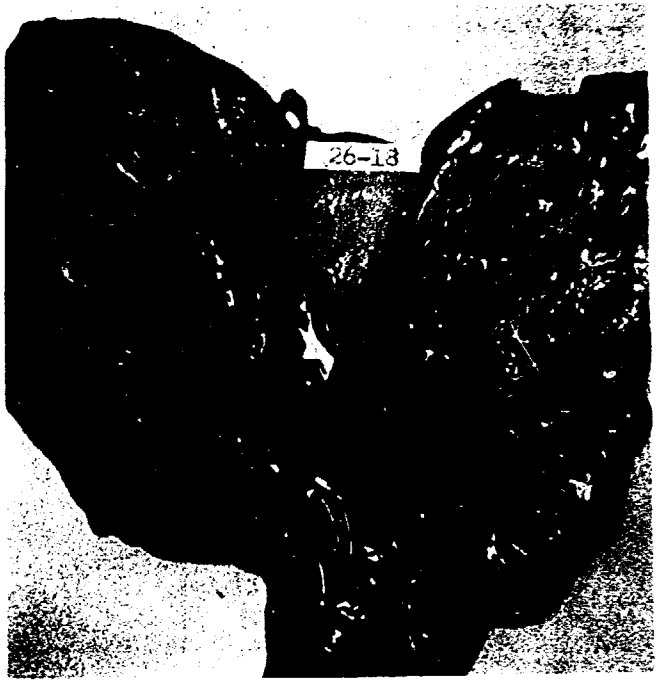

FIGURE 5

Stomach of animal dying 6 days postirradiation with 5.0 kr. The hemorrhagic necrosis is limited to the parietal cell containing area of the gastric mucosa. A thin fibrin membrane covers portions of the necrotic mucosa.

FIGURE 6

Photomicrograph of gastric mucosa of stomach illustrated in figure 4. At the upper left is the mucosal surface. The subjacent lamina propria is hemorrhagic and contains only remnants of gastric glands. There are distorted remnants of gastric glands in the basilar areas.

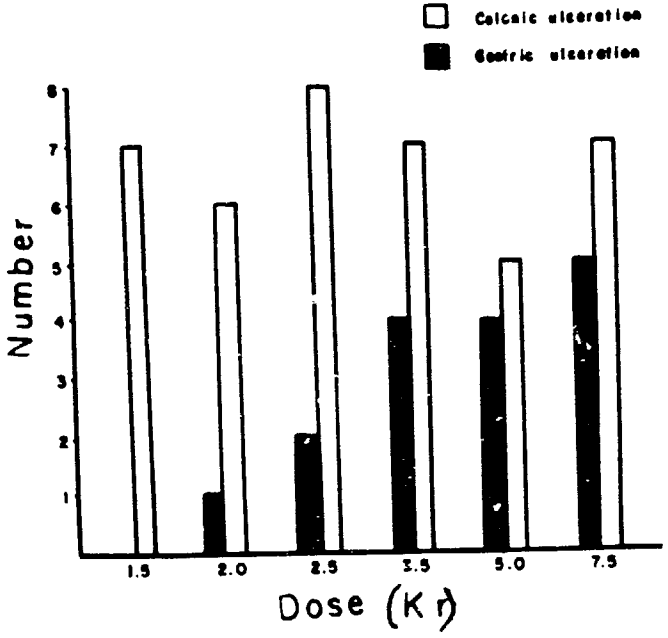

FIGURE 7

This graph shows the incidence of gastric ulceration by dose groups and compares it with the incidence of colonic ulceration. The incidence of colonic ulceration was invariant with dose. The incidence of gastric ulceration increased with increasing dose. The values for the 7.5 kr animals are proportional since there were only 5 monkeys in this group.

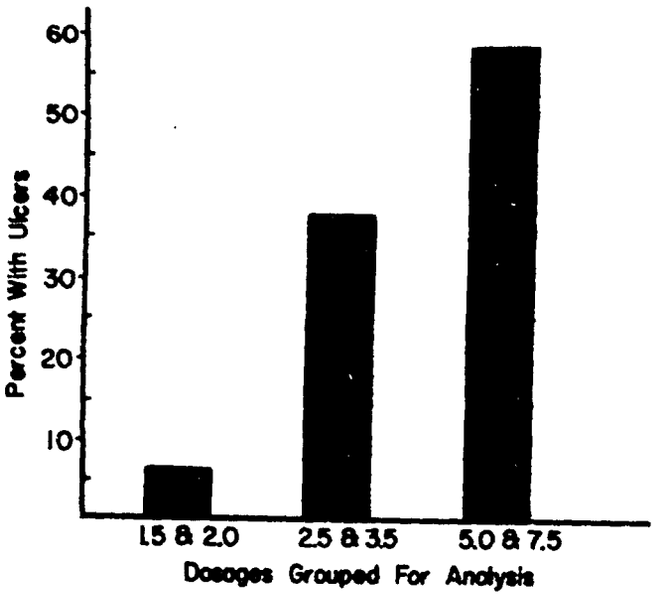

FIGURE 8

Adjacent dose groups are considered together for the purpose of fulfilling the requirements of the chi-square test. There is a striking increase in the incidence of gastric ulceration with relative increases in radiation dose.

Small intestine and colon

Gradations of mucosal atrophy were seen and could be categorized into four types that reflected the severity of cytologic distortion and degrees of epithelial regeneration.

Type I lesions were characterized by severe cytologic distortion of the residual epithelial cells (fig. 10). The mucosal surface was covered by a thin layer of bizarre cells with squamoid features. The voluminous cytoplasm was markedly eosinophilic. The cells often assumed a diamond shape and interdigitated with adjacent similar cells. There were broad fields of dense lamina propria widely separating residual intestinal glands, and the glands themselves were lined by a few flattened cells with atypical nuclei. Quite often only the portion of the glands abutting the muscularis mucosa could be identified in the histologic preparations. The bodies of the glands were so atrophic as to merge imperceptibly with the cellular lamina propria. Even though there was a marked reduction in the number of surface epithelial cells, the physical integrity of the mucosal surface was maintained by a continuous thin covering of squamous-like cells. This lesion is referred to as "squamoid atrophy."

In type II lesions there was also severe cytologic distortion of residual epithelial cells and marked destruction of mucosal glands. However, regenerative efforts were manifested by the proliferation of large, bizarre cuboidal cells along the surface of the mucosa (fig. 11). Mitotic figures were frequent in the surface epithelium, but there was very little regenerative activity in the basilar halves of the mucosal glands, the area usually associated with proliferative activity. This type of lesion is designated "squamoid atrophy with surface regeneration."

Type III lesions resembled type II lesions in that they also exhibited surface regeneration. In addition, the mucosal glands were markedly

FIGURE 9

One of the more severe cases of atrophic gastritis. There are desquamated parietal cells in the glandular lumina. The basilar portions of the glands are mildly atrophic, but the superficial mucous epithelium appears normal. From animal receiving 5.0 kr. Hematoxylin and eosin stain. ×130.

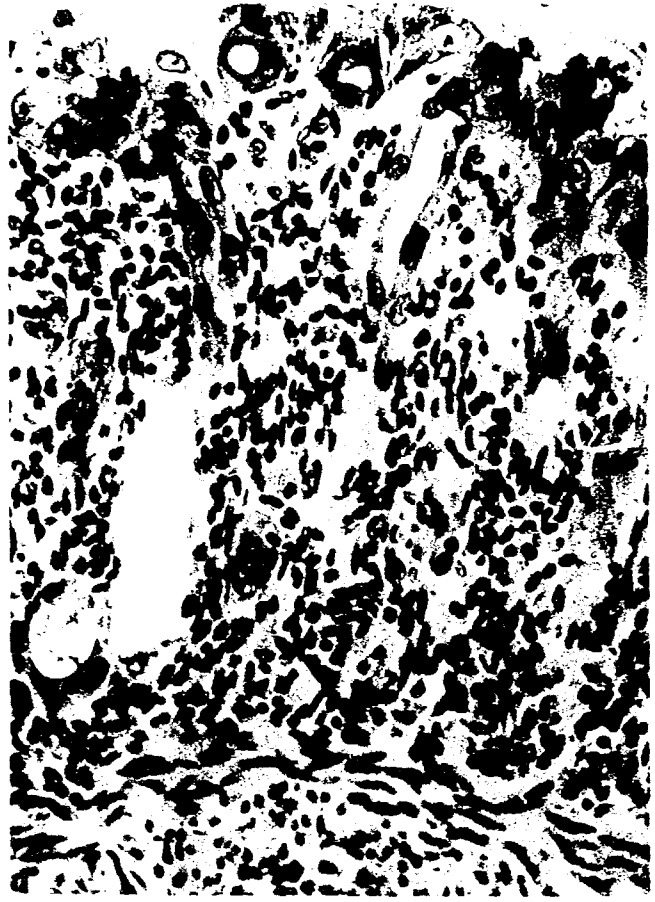

FIGURE 10

Small intestine of animal dying 5 days postirradiation with 3.5 kr. Only degenerating, bizarre, squamouslike cells remain on the mucosal surface. There is severe atrophy of the glands. Hematoxylin and eosin. ×200.

FIGURE 11

"Columnar regeneration" along the surface of the colonic mucosa. This is a type II lesion. Note that the glands are still markedly atrophic. There were occasional mitotic figures in the bizarre epithelium along the mucosal surface. From animal dying 6 days postirradiation with 3.5 kr. ×200.

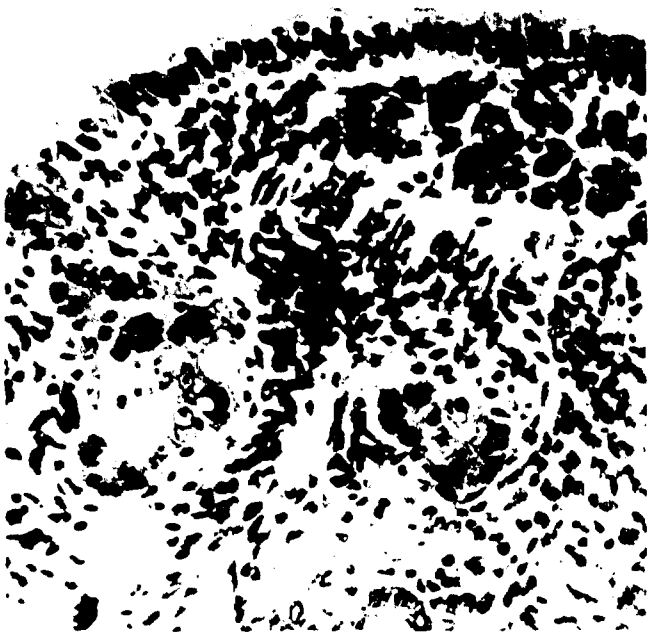

FIGURE 12

A type III lesion (ileum) from animal dying 7 days postirradiation with 2.5 kr. The epithelial cells are atypical, but still retain some of their normal characteristics.

atrophic. However, in type III lesions there could be found in the surface epithelium nests of cells that retained many of their normal cytologic features (fig. 12). The nuclei were basilar in position and uniform in size. The shape of the cells was approximately normal and the cytoplasm was pale pink. Within these nests of cells, the brush border could be identified. Because of these physical characteristics this lesion is referred to as "partial atrophy with surface regeneration."

Type IV lesions were among the most interesting found. In their degree of cytologic distortion and glandular atrophy they were quite similar to the type III lesions. There were, perhaps, slightly larger numbers of apparently normal epithelial cells remaining in the surface epithelium. The distinctive feature that separated this type of lesion from the other three types was glandular regeneration (fig. 13). Although the regenerated glands were moderately distorted, and lined by markedly hyperplastic epithelium, they did represent the first attempt at restoration of a relatively normal architecture. This type of lesion is designated "basilar regenerative" and at times was so extensive as to result in complete re-epithelialization of the intestinal mucosa.

Each of the four types of lesions was found in the small intestine, and their distribution appeared to depend more on *radiation dose* than on survival time. By contrast, in the colon the distribution of the lesion types appeared to be more a function of *survival time* than radiation dose, and types I, II, and IV occurred (figs. 14 and 15).

Even though the histologic alterations in the small intestine and colon were basically the same morphologically, there were striking differences in the gross appearance of the two

FIGURE 13

A type IV lesion (colon) from an animal dying 8 days postirradiation with 1.5 kr. Residual atrophic glands remain, but note the regenerating glandular structures lined by markedly hyperplastic epithelium. There is residual degenerating epithelium along the mucosal surface, but the regenerating epithelium exhibited creeping replacement.

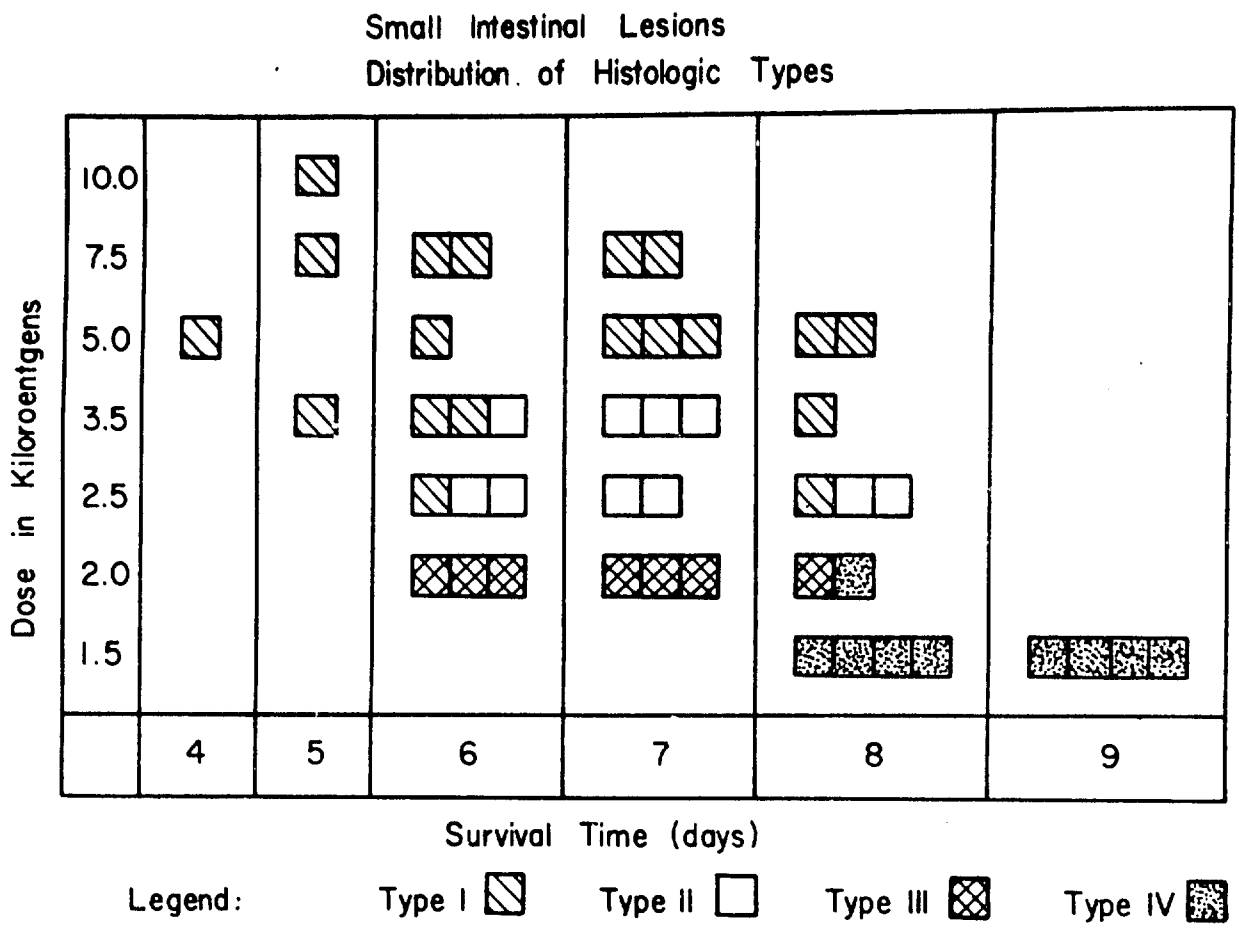

FIGURE 14

There were four basic histologic patterns in the small intestine. Their distribution is more closely linked with dose than time. Each pattern's distinguishing characteristics were dependent upon the degree of epithelial regeneration and the severity of cytologic atypism (see figures 10-13).

organs. In only 2 animals was the mucosa of the small intestine ulcerated. In each instance the ulceration consisted of focal areas of mucosal necrosis located over large submucosal hematomas in the terminal 20 cm. of the ileum (fig. 16). In 4 other animals there were scattered mucosal petechiae. However, the extensive mucosal denudation and congestion, said to characterize intestinal radiation death in other species, failed to materialize in this series of animals. Also, colonic ulceration occurred universally. Thirty-three of the animals had typical hyaline necrosis of the mucosa with superficial erosion and fibrin membrane formation (fig. 17). Each dose group had essentially the same incidence of colonic ulceration (fig. 7).

As in the stomach, the repetitious pattern of ulceration in the colon was the most striking facet of this entity. Two typical examples are illustrated in figures 16 and 17. In figure 18 the incidence of ulceration in the various segments of the colon is depicted. The cecum and ascending colon were far more susceptible to ulceration than the descending colon. Morphologically the colonic ulceration was similar to the gastric ulceration. Bacterial invasion of the submucosa and lymphatics was generally more prominent in the colon and occasionally masses of bacteria were observed infiltrating the lymphatics of the mesentery and pericolonic adipose tissue.

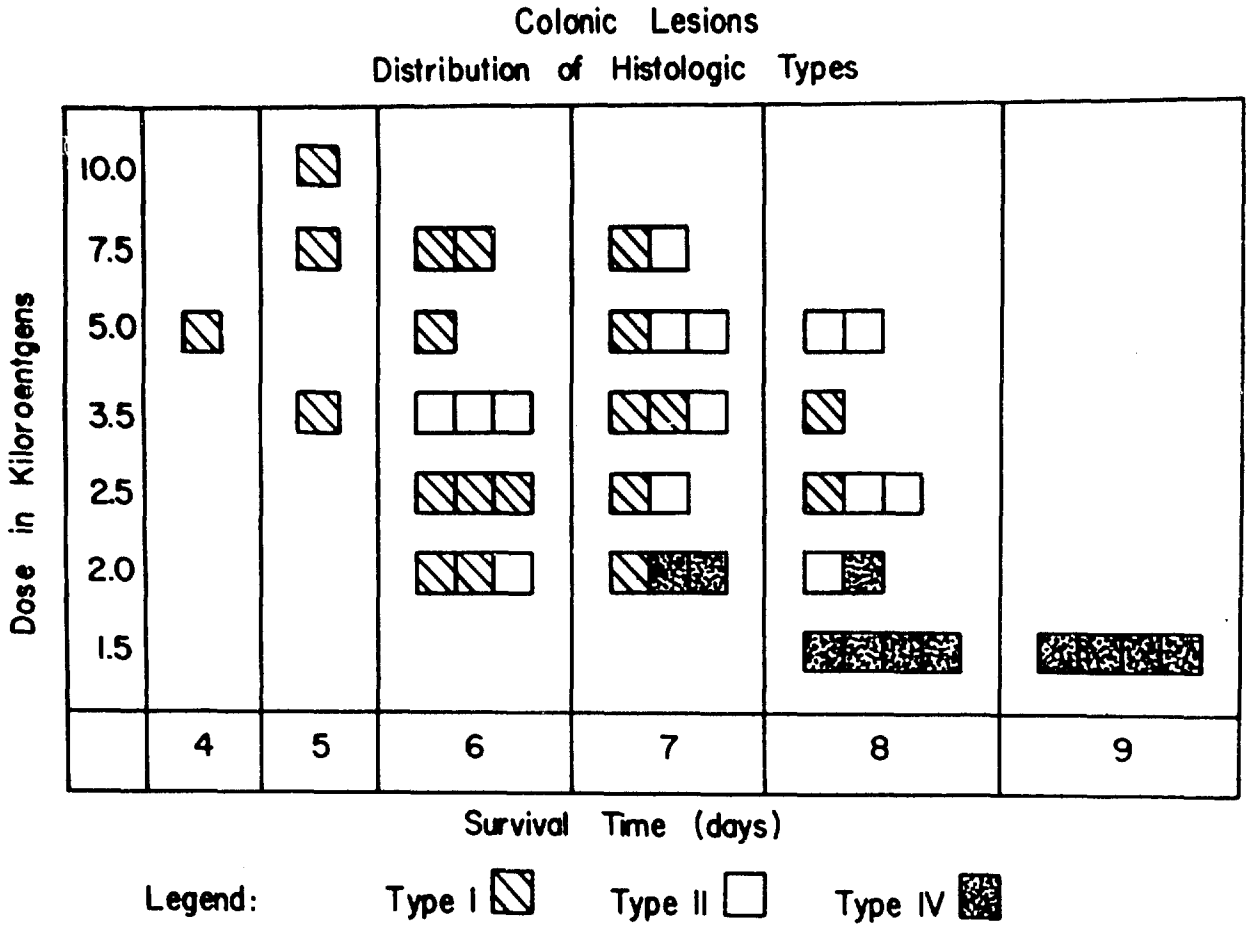

FIGURE 15

Only 3 of the 4 basic histologic lesions observed in the small intestine were found in the colon, and their distribution (with the exception of type IV) was more a function of survival time than radiation dose.

Miscellaneous findings

In most instances the medullary portions of the kidneys were moderately congested and in 4 animals there was extensive interstitial hemorrhage in the renal medulla (fig. 19). Twelve animals had renal cloudy swelling. Typically the involvement consisted of only focal areas of tubular edema. In 4 animals, however, the edema was generalized, and in 2 of these it was severe.

In the mouth, larynx, and esophagus the squamous epithelium exhibited moderate nuclear atypism. The nuclei varied in size and the chromatin was irregularly arranged. Mitotic figures were more numerous than usual. Frequently, colonies of bacteria were adherent to the laryngeal mucosa. In 2 animals the laryngeal mucosa was ulcerated and extensively infiltrated by bacteria.

In approximately one-third of the animals the acinar pattern of the pancreas was almost completely obliterated, and in only rare instances could cells be identified as acinar cells. Replacing the normal architecture were intertwining masses of poorly differentiated cells (fig. 20). These were probably acinar cells that had lost their characteristic cytologic features. The acinar pattern was preserved to some extent, as was revealed by reticulum

FIGURE 16

A case of ulcerative colitis. Note that the first half of the colon is involved, but that the distal half appears grossly normal. Also illustrated in this photograph is one of the two localized areas of ileal hemorrhage observed in the 45 animals. From monkey dying 7 days postirradiation with 2.0 kr.

FIGURE 17

Cecum and ascending colon of animal dying 5 days postirradiation with 7.5 kr. The edematous mucosa contains extensive foci of hemorrhage. The dark areas are hemorrhagic. The light areas are covered by a fibrin membrane.

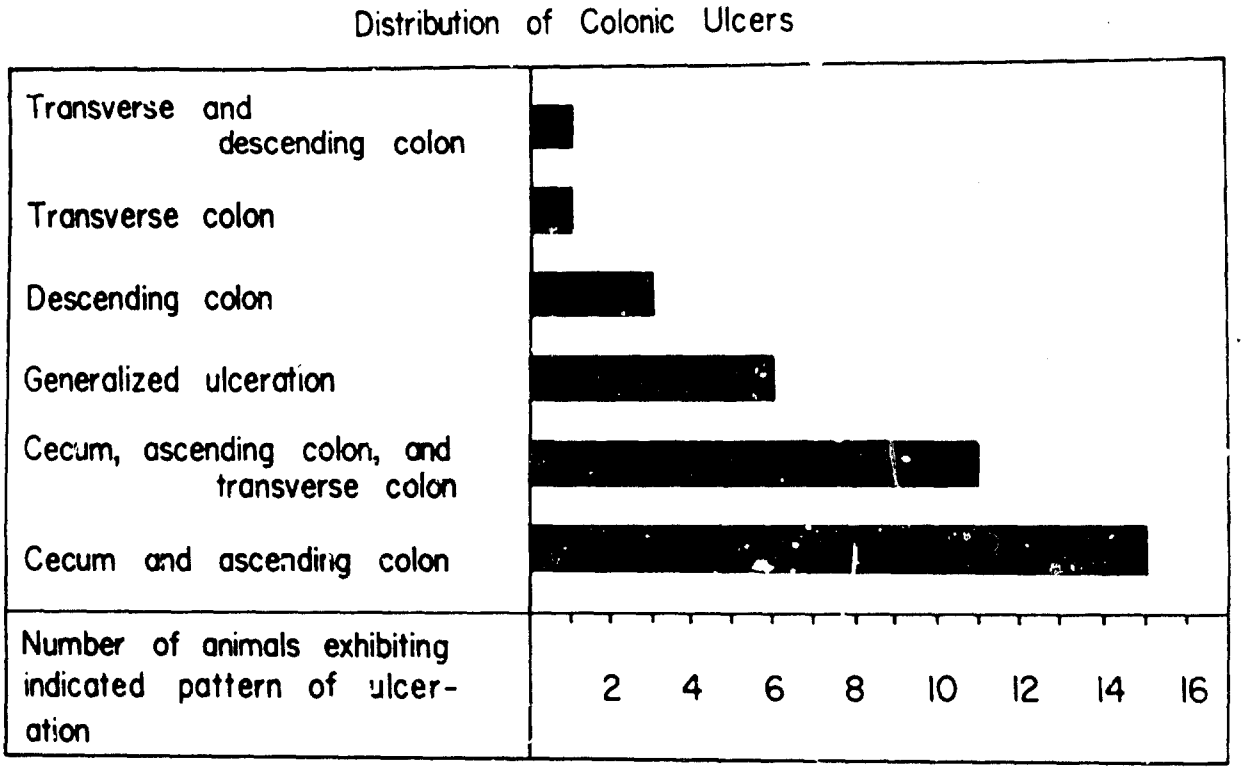

FIGURE 18

Each bar of the graph indicates the total number of animals exhibiting the indicated pattern of ulceration. The predisposition for ulceration in the first half of the colon is striking. In only 5 animals was there ulceration of the colon without involvement of the cecum. On the other hand, in 26 animals the ulcerative process involved the cecum without affecting the descending colon.

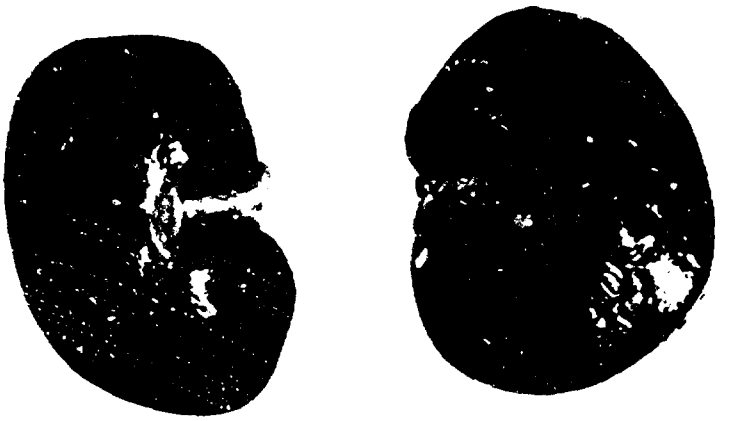

FIGURE 19

In the renal medulla there is marked interstitial hemorrhage. The cortex and inner portion of the medulla are pale and swollen.

stains (fig. 21), but the reticulum was more dense than normal, and delicate strands extended into the centers of the acini.

In all of the animals the bone marrow and lymphoid tissue were severely atrophic.

DISCUSSION

The pathognomonic feature of radiation-induced gastrointestinal death in the monkey is severe radio-enterocolitis (11). All segments of the intestine and colon appear equally sensitive. The rectum occasionally shows less damage than the other portions of the large bowel. In contrast to some of the more common laboratory animals the physical integrity of the mucosal epithelium is maintained even though the residual cells are atypical and markedly reduced in number.

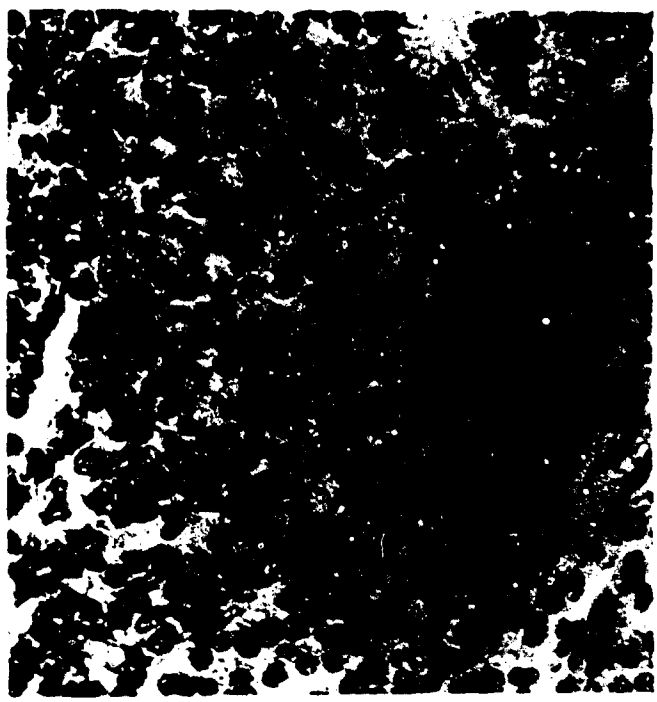

FIGURE 20

Pancreas of animal dying 5 days postirradiation with 3.5 kr. The acinar cells have lost all of their normal characteristics. The acinar pattern is obliterated. Hematoxylin and eosin, ×300.

FIGURE 21

Reticulum stain of pancreas illustrated in figure 20. The reticulum is dense, but reveals that the alveolar pattern of the pancreatic tissue is preserved.

Animals irradiated with acute doses of gamma radiation sufficient to produce death within 3 days fail to develop the characteristic cytologic atypism in the intestinal epithelium (11,13,16,17). In addition, total-body irradiation with less than 850 r (± 100 r) is not sufficient to induce the typical cellular changes (11). Animals irradiated with 900 r of x-ray from a 250 kvp Picker therapy machine will occasionally exhibit focal areas of epithelial changes (18). Optimum doses of radiation (1.5 to 7.5 kr) result in death of the animal between 4 and 9 days postirradiation.

The histologic alterations produced in the epithelium of the small intestine and colon are qualitatively the same and can be divided into four distinct groups that are a measure of cytologic alteration and degree of epithelial

regeneration manifested at the time of death. Type I lesions exhibit severe cytologic distortion and no regeneration. They represent the most severe degree of damage and are referred to as "squamoid atrophy." Type II lesions are also characterized by severe cytologic distortion, but in addition, exhibit the phenomenon of surface regeneration. Accordingly, this type of lesion is designated "squamoid atrophy with surface regeneration." Type III lesions closely resemble type II lesions with the exception that a moderate percentage of surface epithelia retain some of their normal cytologic features; for that reason, this condition is described as "partial atrophy with surface regeneration." The type IV lesions represent the most advanced stage of epithelial regeneration. The degree of cytologic atypism present is comparable to that found in the type III lesions. However, the characteristic feature is the presence of regenerating glandular forms.

All four types of lesions are found in the small intestine and their distribution is to a great extent dependent on total radiation dose (fig. 14). On the other hand, only types I, II, and IV are found in the colon. This may be due to the inherent differences in architecture in the two organs; that is, the cells that normally are the last to lose their characteristic cytologic features after irradiation are the epithelial cells covering the surface of the mucosa. The villi of the small intestine possess far more surface cells than comparable structures in the colon. Hence, there is numerically a better chance of finding normal cells in the former than in the latter. There are reasons, however, to suspect that the absence of type III lesions from the colon may be real rather than artifactitious. One such indication in the colon is the fact that the distribution of the various types of lesions is more dependent on survival time than on total dose received (fig. 15). Since the various categories reflect to a certain extent the degree of regeneration present, the pattern of distribution within the dose range employed would suggest that the regenerative power of the small intestine is compromised at a lower dose level than that of the colon. Since the various categories are also a measure of cytologic distortion, it may be inferred through similar reasoning that higher total doses of gamma are required to obliterate all normal cytologic detail in the small intestine than in the colon.

Worthy of special comment is the phenomenon of basilar regeneration observed in the small intestine and colon. In both organs this lesion was distributed as a function of dose. There is a time correlation, however, since a certain lag period is required for the development of any lesion following the initiating trauma. The dose relationship is emphasized by the fact that every 1.5 kr animal exhibited extensive basilar regeneration. In contrast, only an occasional regenerative gland was found in animals receiving more than 2 kr. In addition, on the 8th day postirradiation 4 animals exposed to 1.5 kr died, exhibiting basilar regeneration, while 7 other animals receiving between 2.0 and 5.0 kr failed to exhibit this phenomenon (figs. 14 and 15).

In spite of the qualitative similarity in the epithelial changes in the small intestine and colon, there was a striking discrepance in the incidence of ulceration in the two organs. Only two ileal ulcers were found, and these appeared as deeply penetrating defects over large submucosal hematomas in the lower 20 cm. of the ileum. On the other hand, colonic ulceration occurred in 33 of the subjects. The incidence of colonic ulceration was invariant over the dose range tested (fig. 7).

Aside from digestive function, one of the most obvious differences between these two segments of the gastrointestinal tract is the bacterial flora. While the small intestine is not completely sterile, the bacterial flora is quite insignificant in comparison to the colon (19). In addition to the marked difference in the incidence of mucosal ulceration in the small intestine and colon, the tremendous predilection of the upper half of the colon as compared to the lower half is interpreted as an indication of the primary role of bacteria in producing ulceration.

The role of the abrasive action produced by the passage of the fecal stream has been considered of primary importance by some investigators. This was particularly emphasized

by Friedman (10) in a study using colostomies to divert the fecal stream in irradiated rats. He did not, however, completely discount the bacterial factor. In the current study the mechanical factors are regarded as secondary. The reasons for these conclusions are threefold. Both the small intestine and colon experienced a flow of particulate matter. Contents of the small intestine are relatively fluid, but so are the cecal contents. Firm fecal material, which possesses more abrasive properties than liquid fecal material, is usually not formed until at least the level of the hepatic flexure is reached. Hence, the area of maximum ulceration occurs at the point of maximum stasis of liquid fecal material and not in the area subjected to the maximum abrasive trauma. It had also been shown in some species that the bacterial content of the cecum is about one hundred times more concentrated than that of the sigmoid (19).

It is reasonable to assume that an acute dose of 10 kr of gamma radiation would be at least as efficient as 7.5 kr in producing gastric ulceration. It has been observed, however, that animals irradiated with 10 kr or more die within 3 days and fail to develop ulcers (13, 16, 17). It is concluded, therefore, that at least 4 days are required for the development of such lesions. After 4 days, the incidence of ulceration is a function of dose rather than time. As the total dose is increased, the incidence of gastric ulceration is increased. The finding of a significant negative correlation between ulcers and time to death (−.576) with the influence of dosage removed is interpreted as meaning that those animals which develop ulcers die sooner than those animals which do not develop ulcers, irrespective of dosage. This observation assumes greater significance when it is noted that the incidence of ulceration increases as the radiation dose is increased. Under these conditions, ulceration becomes an important factor in determining the slope of the "dosage versus time mortality curve" (fig. 3). Radiation dose nevertheless remains a determining factor, as attested by the lower significant correlation (.3909) between dose and death, when the relationship of ulcers to both dosage and death is extracted.

Since gastric ulceration is limited to that portion of the mucosa richest in parietal cells, it appears probable that selective cell damage is an important factor in regulating the repetitious pattern of the lesions. The predilection of this particular cell for radiation damage is emphasized by the pattern of mucosal atrophy as found in this experiment, as well as by the work of others (11,13,16,17). However, there are two other facets to the problem which cannot be disregarded. First of all, although in their most severe form the ulcers assume a butterfly configuration, the smaller lesions are limited to the mucosa of the greater curvature, the most dependent portion of the stomach. Secondly, among apparently normal animals sacrificed at random in this laboratory bacteria are not infrequently found in the lumina of the gastric glands richest in parietal cells. Hence, the same principles applicable to the pathogenesis of colonic ulcers are thought to affect also the development of gastric ulcers under the conditions of this experiment. That is, intrinsic bacterial flora are able to penetrate the damaged mucosa and produce tissue necrosis and hemorrhage. The particulate matter contributes more to ulcer production through its presence which favors bacterial growth than through its tendency to scrape cells off the mucosa as it passes along the gastrointestinal tract.

SUMMARY

Forty-four monkeys irradiated with 1.5 to 7.5 kr of cobalt -60 (gamma) radiation died between 4 and 9 days postirradiation. The greatest percentage of deaths occurred on the 6th, 7th, and 8th days. The mean survival time was 6 days. The most prominent findings at autopsy were gastric and colonic ulceration. Colonic ulceration occurred in 33 of the animals and its incidence was invariant with radiation dose over the dose range tested. Gastric ulceration occurred only 14 times. Its incidence increased as radiation dose increased. This observation was analyzed statistically. Evidence presented suggests that bacteria play a dominant role in the production of gastric and colonic ulceration following supralethal doses of radiation.

Severe mucosal atrophy occurred in both the small intestine and colon. It could be divided into four basic types that reflected the severity of cytologic distortion of the epithelial cells, and the degree of epithelial cell regeneration. In the small intestine, the distribution of the lesion types was a function of radiation dose; in the colon the distribution was a function of survival time. The significance of these variations is discussed.

The statistical analyses were performed by Dr. A. A. McDowell, Department of Psychology, the University of Texas.

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