FINAL REPORT

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TITLE OF PROJECT: The Effects of Ingestion of Large Doses of Radioactive Elements on the Alimentary Canal (Including Mouth, Teeth and Periodontal Structures and Other Vital Organs).

Introduction:

The gastrointestinal tract plays an important, if ill-defined, role in radiation injury. External body radiation is most injurious when administered to a volume encompassing appreciable segments of the stomach and intestines. Lesions in the stomach wall have been reported even in those instances where radiation was excluded from striking this organ. Such evidence has led some authors to conclude that certain structures are vulnerable to both direct and to indirect actions of radiation. The stress concept of Selye has lent credence to the concept of indirect injury to structures because of the similarity of many such lesions with those induced by radiation. The lymphoid tissue containing structures of the body are among the most vulnerable in this respect.

Objectives:

General: The general purpose of this study was to study the effects of ingested radioactive substances on the gastrointestinal tract in general and the oral region in particular.

Specific: More specifically it was desired to determine whether lesions similar to those reported found in the stomach and intestine could be discerned in the mouth. A further purpose was to analyze the effects of local irradiation of the G. I. tract without the presence of an appreciable external irradiating source. In view of the plan to irradiate locally the alimentary canal it was also deemed worthwhile to analyze the effects of such irradiation on the thymus, spleen and adrenals which are so intimately concerned with stress.

Technical Findings:

Preliminary to the actual irradiating of the animals chosen for the study (Long-Evans rats), we had first to select an isotope and dosage schedule.

Selection of Isotope - Absorption: Practical considerations governed the choice of the isotope. The first prerequisite of the irradiating source to be used was that it not be absorbed into the circulation. A property such as this would have immediately defeated the aim of confining the ionizing rays to the tissues directly concerned. There was evidence that Zr^{95} Nb^{95} were not absorbed and these elements had an additional practical value from the fact that they actually were abundantly produced by fission explosions. Data reported in the statement of July-December 1953 indicated 93% was passed through the digestive tract unabsorbed. The least amount recovered was 69% while the maximum value was 107% when compared with the dose as measured prior to administration. These data suggest that absorption of Zr^{95} and Nb^{95} mixtures is erratic and in most cases negligible.

Chemical Form: A second requirement was that the isotope was obtainable as carrier-free material since excess carrier might prove to be an uncontrolled variable. Carrier-free fission products, however, are best handled as complexed salts inasmuch as the uncomplexed atoms tend to plate out on the walls of the vessel. Data in the report of July-December 1951 indicate that the use of ceresin wax coatings does not significantly reduce the loss of radioactivity due to plating out. It was, therefore, decided to limit efforts to the use of complex carrier-free material only.

Distribution of Ionization: The physical properties of the radioactive emissions of Zr^{95} and Nb^{95} were given in the report of January-June 1951.

Since it was intended to confine the bulk of the ionization to the G.I. tract it was evident that beta emitters had to be used. The maximum energy of these beta particles had to be small enough to allow almost the entire path of ionization to occur within the cells of the gut. Zr^{95} beta particles have a maximum range of 1.25 mm. whereas Nb^{95} electrons penetrate tissue no further than 0.4 mm. Calculations give an estimate that Zr^{95} beta particles in tissue would produce over the total path of ionization an average distance of 0.3 microns between ion clusters. This means that ionization would be intense enough to occur in every cell along the path of the electron.

Dosage Schedule:

The selection of the dose was largely based on values given in the literature until some experience proved otherwise. Bloom, in an incomplete series of animals, reported that values of about 20-30 microcuries per gram of body weight of fission products given by gavage produced significant lesions in the lymphatic organs. With 200 gram rats a dose of 4-6 millicuries would be equivalent to the levels employed by Bloom. Inasmuch as the problem of acute ingestion of radioisotopes, as may confront Naval personnel, rather than long term cumulative doses was to be studied, the dose decided on was to be ingested as a single large dose. The use of the stomach tube in previous studies has a twofold influence which excludes its use in the present one. Firstly, it allows the source of radiation to by-pass the principal object of this study, the mouth.

Secondly, it introduces into the stomach all at once the entire dose of isotope. Drinking or eating obviously cannot do this and the dose received under these more natural circumstances is of necessity divided. There is thus a dual reason for fractionation of the ingested material. The first is the periodic nature of the eating and drinking habits of the rat. The second is the rather complex movements or currents of the semi-liquid contents of the gastro-intestinal tract. An estimate of the combined effect of these two factors was furnished in the report of July-December 1953.

It soon became apparent from histopathologic surveys that the oral region was not showing abnormal changes even under the largest dosages used. Analyses of the rate of passage of a food bolus demonstrated that the duration of exposure to the ingested isotope was significantly smaller in the mouth and esophagus than in the remainder of the alimentary canal. Graphs depicting this were included in the report covering the period July 1, 1953 to December 31, 1953.

Beginning with levels of 2 millicuries and ending at 24 millicuries per animal a range of doses from 10-125 microcuries per gram of body weight was administered to a group of Long-Evans male rats. Injury was observed macroscopically and microscopically in the upper 1/5 of this range only.

Effect on the Gastrointestinal Tract:

1) Feces Moisture Content: Table 1 reveals an increase in the percent of water in the feces at the highest range of doses employed. The value at this level of ingestion is almost twice the control or normal values. This may be regarded as a measure of the degree of diarrhea which in turn is an index of the injury sustained by the intestinal tract.

Table 1

The Effect of Increasing Ingested Doses of Zr^{95} Nb^{95} on Food and Water Consumption and on Moisture Content of Feces (Average of 6 animals)

Consumed dose, microcuries per gram	Grams of food eaten per 100 gms. body wt. per day	cc H_2O consumed per 100 gms. body weight per day	% of moisture in 24 hr. samples of feces
1-25	10.3	13.9	24.2
26-50	11.4	12.4	22.7
50-75	8.25	11.2	25.6
100-125	5.45	10.4	41.7
Control	10.8	12.1	25.8

2) Macroscopic Findings:

a. Droppings from the third day on of the animals receiving the 100-125 microcurie per gram dose were almost always bloody.

b. The lesions which were found at autopsy were blood clots with underlying ulcerations. These could be observed in the pyloric portion of the stomach and the large intestine. The cardiac half of the stomach which is lined by stratified squamous epithelium showed no abnormality, nor did the cecum and small intestine. In general the amount of morphologic damage was less than expected from the degree of bloody diarrhea observed. The lesions occurred as solitary depressions in the mucosa with sharply demarcated, unraised borders.

c. No macroscopic or microscopic abnormalities were noticed in the mouth or esophagus of any group of animals.

3) Microscopic Findings:

The stomach ulceration seen in Figure 1 may be contrasted with the normal architecture of the pyloric stomach of the rat shown in Figure 2. The columnar epithelial cells have been shed and the connective tissue cores have been laid bare. The lesion extends past the muscularis mucosae which is interrupted in the center of the figure. Maximum penetration of the lesion is about at the level of the lamina muscularis. The heavy component of the nuclear material seen at the base of the ulcer takes two forms: nuclear debris from lysed cells and inflammatory infiltration. It is noteworthy that inflammatory reaction is not sparse as in instances where total body radiation has been employed.

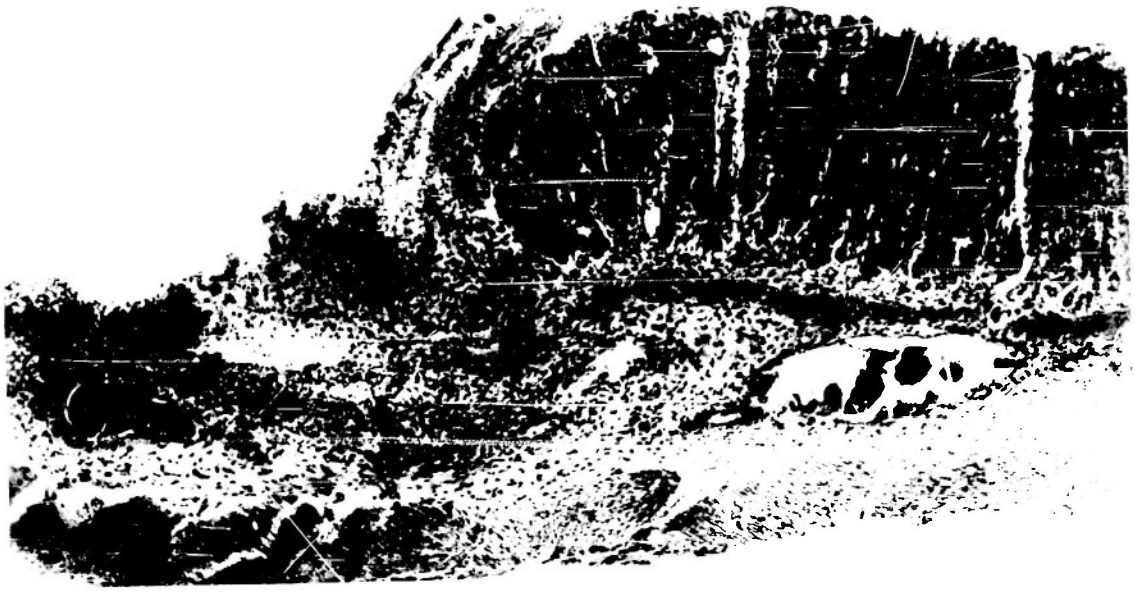

Figure 1

Figure 2

Figure 3 shows a denuded section of large intestine showing the exposed connective tissue cores now bordering directly on the lumen. Contrasted with this is Figure 4 which is from a normal animal. In the large intestine the lesion is more superficial being confined to the layers superficial to the submucosa. Cellular reaction is absent although nuclear debris is abundant.

Figure 3

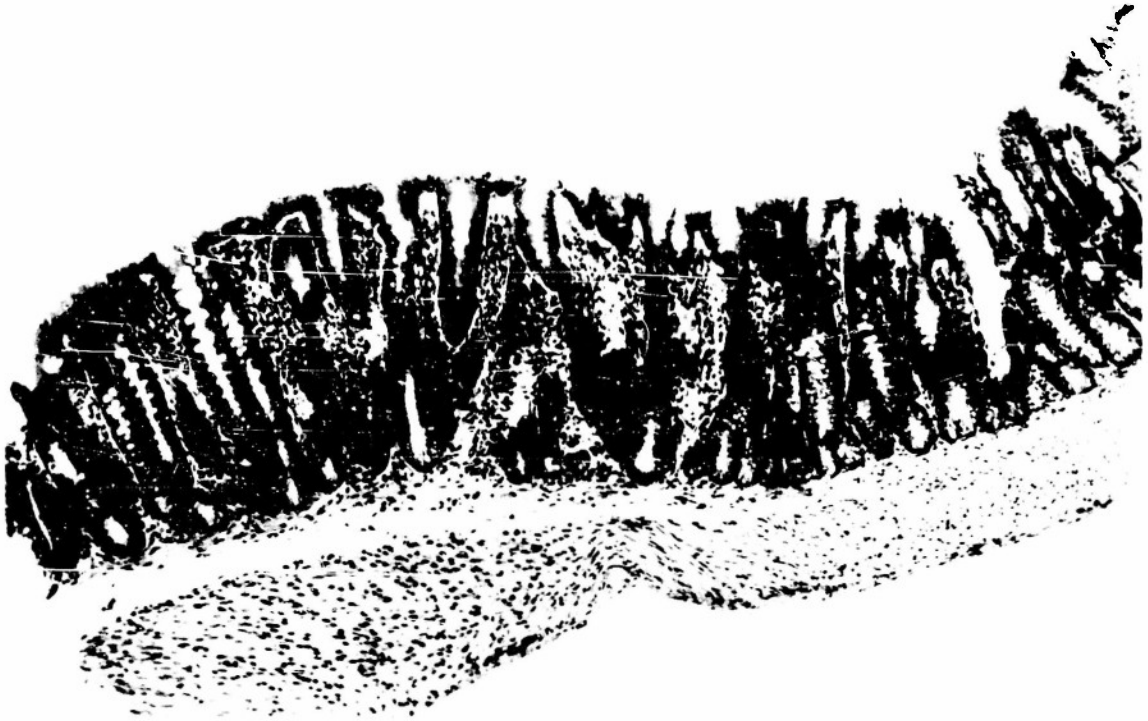

Figure 4

In the small intestine two points may be noted (Figure 5). The regularity of the spindle shaped nuclei and the even height of the columnar cells is evidence that no stretching of the epithelium has occurred. The location of the goblet cells in the lower portions of the glands, however, is evidence that some interference with the movement of these cells has taken place. It is customary for goblet cells to reach maturity at the distal half of the villus resulting in their appearance predominantly in the peripheral portion of the crypt. Figure 5 illustrates what happens if the peripheral movement of the cells lining the mucosal surface is retarded by a temporary interference with the mitoses ordinarily taking place in the depths of the crypts. The goblet cells have arisen from a source other than the nest of the epithelium and have matured normally. During their maturation they were not pushed along the surface of the villus by the continual formation of new cells at the base of the cript as they normally would be. Radiation has apparently temporarily inhibited the mitoses responsible for the new cells. Since cells continue to be shed every few days, in more severe retardation a deficiency results in the epithelial lining with subsequent stretching of the cells to resemble squamous epithelium. This has not occurred in this specimen.

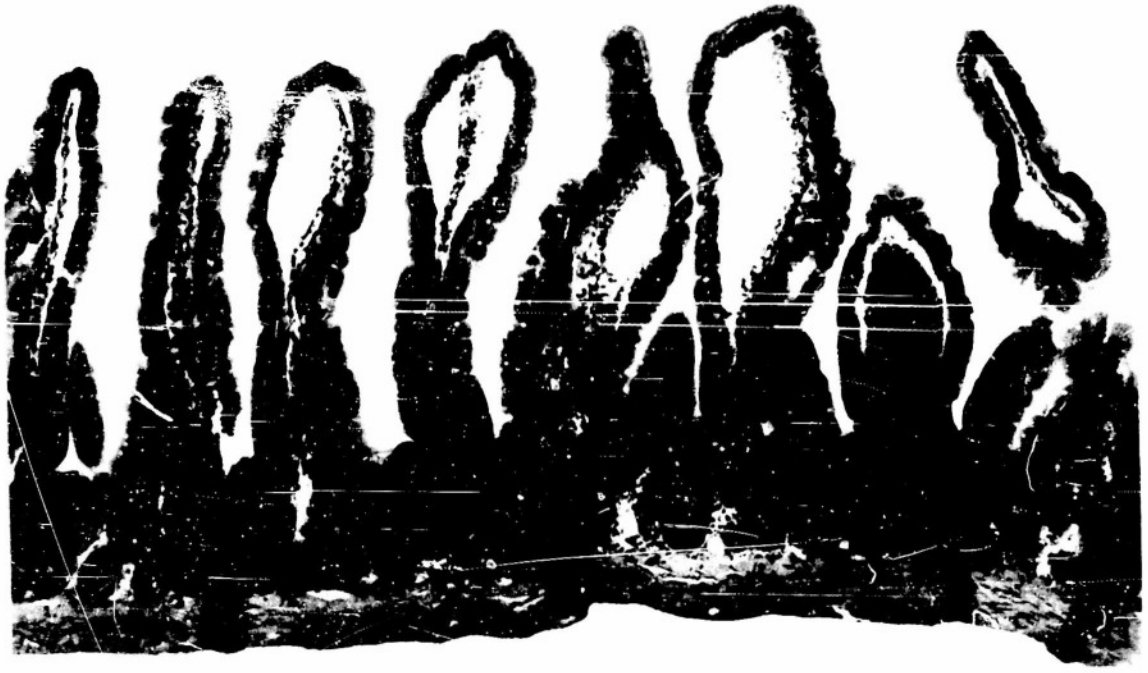

Figure 5

Figure 6 is a cecum specimen showing only few changes due to irradiation. The epithelium is intact and shows normal relationships to the underlying tissues. Some edema may be seen in the submucosa in addition to engorged vessels. Cellular infiltration is noteworthy although this is common in the cecum of normal animals as well.

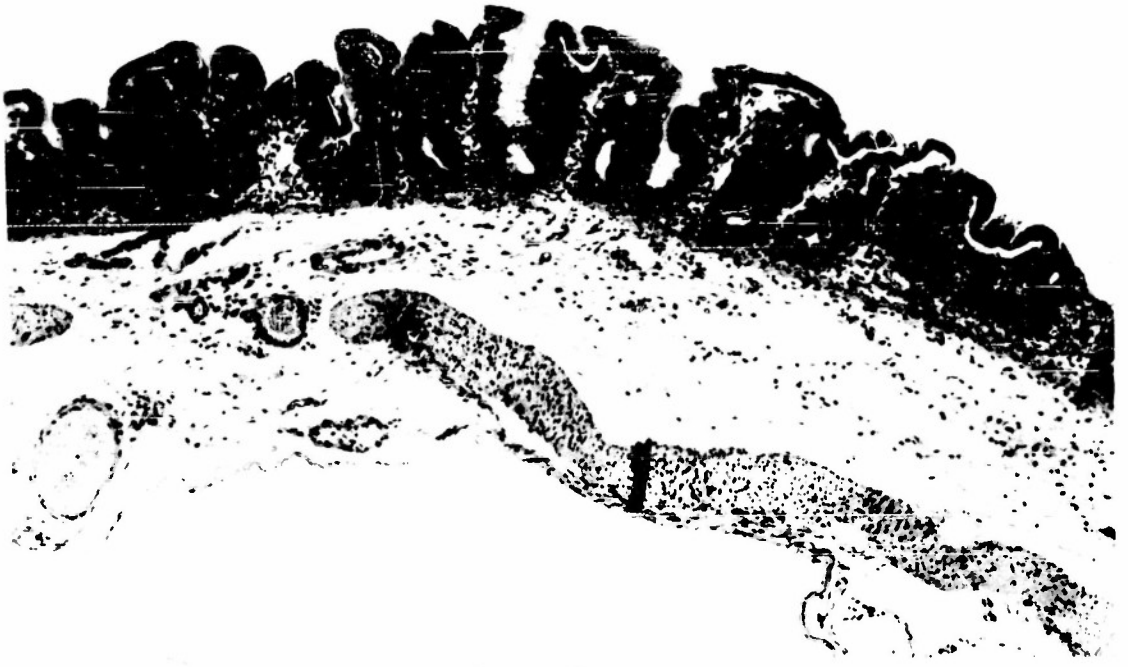

Figure 6

Figure 7 shows a tongue section which is apparently normal in every respect. The lower portions of the alimentary canal of this animal showed changes similar to those reported above.

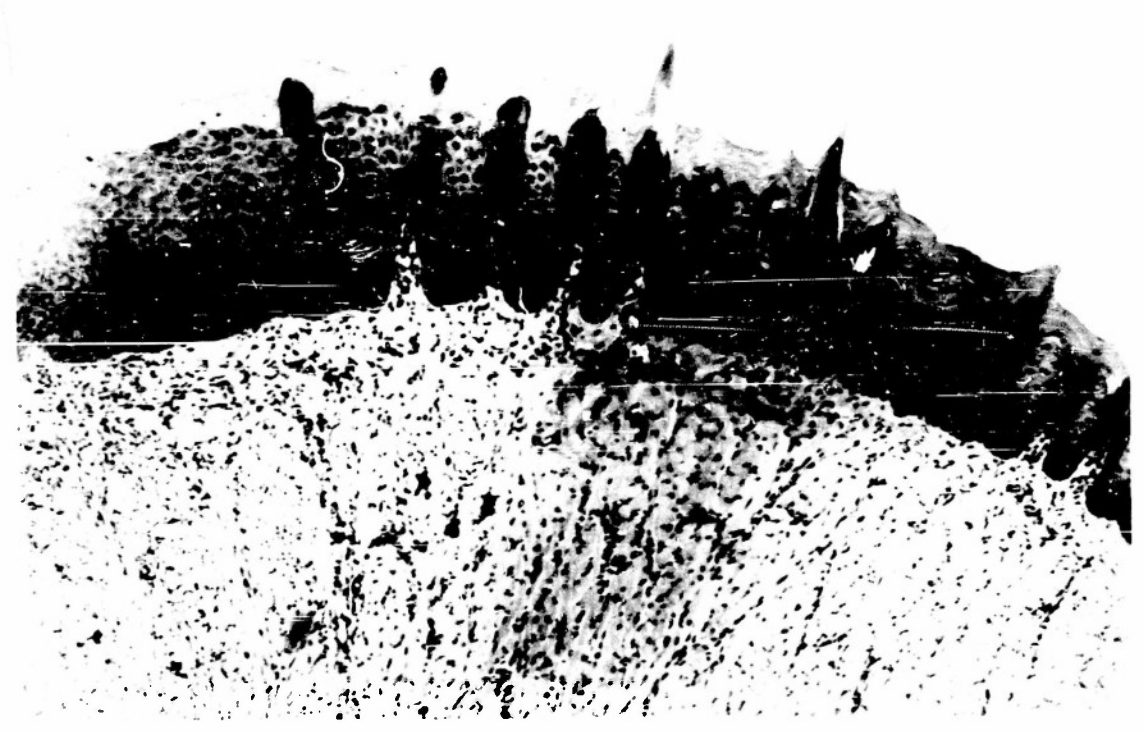

Figure 7

Effects on General Metabolism:

a. Food and Water Consumption: Food intake is markedly decreased out of proportion to loss of body weight in the injured animals. This is indicated in Table 2 . Water consumption remains at a normal level in the injured animals in spite of the increased loss of water in the feces and diminished food intake.

Table 2

The Effect of Ingestion of Increasing Amounts of Zr^{95} Nb^{95} on the Per cent of Body Weight Represented by the Spleen, Thymus and Adrenals (Average of 6 animals)

Consumed Dose Microcuries per gm.	Spleen	Thymus	Adrenals
1-25	0.176	0.154	.0139
26-50	0.222	0.131	.0136
50-75	0.178	0.134	.0153
100-125	0.102	0.0628	.0185

b. Wet Weights of Spleen, Thymus: At radiation levels sufficient to produce overt injury the splenic and thymic fresh weights are significantly reduced from normal values. This is in keeping with the non-specific effects of radiation on lymphoid tissues.

c. Wet Weights of the Adrenals: The two adrenal glands weigh more following the highest doses than after the lower and apparently non-injurious levels. Their color is red rather than pale or white as in the more nearly normal animals.

Conclusions:

1. Ingestion of fission products as single large doses brings about severe injury to the gastrointestinal tract which may result in death.

2. The oral structures are among the least affected by this health hazard. It is anticipated that the presence of oral lesions from ingestion of radioactivity would be preceded by signs of injury elsewhere in the gastrointestinal tract.

3. Confining the radiation to the immediate vicinity of the alimentary canal results in injuries which are similar to those produced by external radiation. These include ulceration, hemorrhage and diarrhea.

4. Local irradiation of the stomach and intestines results in reduction in size of the thymico-lymphatic apparatus and increased weight of the adrenal glands.

5. Local irradiation of the gut produces ulcerations which are not characterized by sparse cellular reaction.

Reports and Publications:

a. Reports: July 15, 1951
March 31, 1952
January 8, 1953
July 1, 1953
February 1, 1954

b. Publications:

1. A Rapid Radioautographic Technique for Combined Calcified and Soft Tissues; Myers, H., Jennings, E. and Becks, H. J. D. Res., 31:416, June 1952

2. The Uptake of Ca^{45} by the Teeth and Mandibles of Rachitic, Young Growing and Adult Rats; Myers, H.M., Thompson, D.M. In Press

3. The Comparative Turnover Rate of P^{32} in Normal and Deficient Rats' Teeth and Bones During Recovery from Phosphorus Deficiency; Myers, H. In Press

4. The Location of Radiocalcium in the Mandibular Incisor and Adjacent Structures of the Rat; Myers, H.; In Press, J.D.Res.