become obvious, from mere macroscopic inspection, that these steroids fail to inhibit the inflammatory reaction when administered at the same dose level as the hydrocortisone acetate (Fig. 4 and Table III).

Table III indicates that, at this dose level, neither the formation of exudate, nor the development of the granuloma-pouch wall were significantly altered by these steroids. In this 9-day experiment, irrespective of treatment, the volume of the residual air is higher in all groups than in the first two 14-day experiments.

These findings, concerning the predominantly exudative, hemorrhagic response to croton oil, essentially confirm earlier animal experiments on the effect of gluco-corticoids upon inflammatory reactions in general(3-6). However, the use of a new technic permitted the experimental production of an inflammatory focus whose initial size and shape are always identical. It also made possible the objective, quantitative, separate determination of exudate and granuloma tissue formation, the recovery of the eliciting irritant and the accurate introduction of hormone preparations into the granuloma wall proper.

Summary. 1. Using the "granuloma pouch" technic, it was possible to produce very large amounts of inflammatory tissue and fluid (corresponding, in some cases, to as much as 25% of total body weight) in the rat, without interfering with the general well-being of the animal. 2. The introduction of small amounts of hydrocortisone, directly into the wall of the pouch, completely prevents the development of these inflammatory structures. 3. Introduction of the same amount of hydrocortisone into the lumen of the pouch, or into connective tissue at a distance of only about one mm from the pouch, is virtually ineffective. 4. The croton oil used to produce these granuloma pouches retained part of its irritating effects, even after a sojourn of 14 days, in hydrocortisone protected connective tissue. Although here it failed to cause inflammation, it still produced considerable damage, with hemorrhagic necrosis, when it was introduced into the unprotected connective tissue of other recipient animals.

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Effect of X-Irradiation on Weight and Contents of Rat Stomach, Small and Large Intestine.* (20109)

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The vulnerability of the gastrointestinal tract to ionizing radiation has long been recognized. Quastler *et al.*(1), Cronkite(2), Bond (3), and others, have demonstrated the importance of the relationship of gastrointestinal damage to early deaths in animals seen after large doses of total body irradiation. Even with relatively low doses, the extreme sensitivity of the system to radiation has been demonstrated by certain functional changes, such as increased tone and amplitude of contractions of the rat intestine which occurred during irradiation or immediately thereafter, followed by a period of atonicity and lack of motility lasting for several days(4). Pharma-

* The opinions or assertions contained herein are the private ones of the author and are not necessarily to be construed as official or reflecting the views of the Navy Department or the naval service at large.

TABLE I. Effect of 500 r X-irradiation on (a) Weights of Stomach, Small and Large Intestine of the Rat, and (b) Contents of These Components.

		Stomach			Small intestine			Large intestine		
Days after irradiation	No. of rats	Mean wt, g	% diff. from controls	P	Mean wt, g	% diff. from controls	P	Mean wt, g	% diff. from controls	P
					(a) Wt of organs					
Controls	13	1.034			4.804			2.049		
1 – 2	10	.888	—14.1	<.01	3.458	—28.0	<.01	1.586	—22.6	<.01
2 – 3	"	.872	—15.7	<.01	3.150	—34.4	<.01	1.565	—23.6	<.01
3 – 4	"	.890	—13.9	<.02	3.856	—19.7	<.01	1.832	—10.6	<.2
4 – 5	"	.799	—22.7	<.01	4.590	— 4.4	<.5	1.894	— 8.2	<.01
5 – 6	"	.901	—12.9	<.02	4.765	— 0.8	>.9	1.989	— 2.9	<.7
7 – 8	"	.987	—12.2	<.6	4.582	— 4.6	<.5	1.991	— 2.8	<.7
					(b) Wt of contents					
Controls	12	1.71			4.05			4.89		
1 – 2	10	4.65	+171.3	<.01	2.94	—27.5	<.4	3.65	—25.5	<.1
2 – 3	"	3.57	+108.3	<.05	3.06	—24.5	<.4	4.24	—13.4	<.4
3 – 4	"	2.47	+ 44.1	<.4	3.66	— 9.6	<.8	4.05	—17.3	<.5
4 – 5	"	.76	— 55.6	<.2	2.96	—26.9	<.4	4.55	— 7.0	<.7
5 – 6	"	3.91	+128.1	<.01	6.22	+17.5	<.3	6.75	+37.9	<.02
7 – 8	"	3.91	+128.0	<.02	5.56	+13.0	<.4	5.35	+ 9.2	<.6

cological studies of these changes indicated that an autonomic imbalance of the enteric nerve elements of the gastrointestinal tract was induced by radiation. Such functional changes are no doubt related to the early post-irradiation gastrointestinal symptomatology such as anorexia, weight loss, diarrhea, etc.

On the basis of histo-pathological observations it is generally conceded that the small intestine is the most sensitive part of the gastrointestinal tract to ionizing radiation(5, 6). In recent experiments(7) the author has noted a marked weight loss of the small intestine of the rat following low lethal doses of x-radiation. In the present study, the relative sensitivities to radiation of the stomach, small intestine and large intestine of the rat are expressed quantitatively in terms of relative weight changes produced in these components by single acute doses of x-irradiation. In order to evaluate the role of edema or dehydration, water content of the tissues was also studied. In addition, changes in weight and character of the contents of the various components of the gastrointestinal tract were noted for correlative purposes.

Materials and methods. Relative changes induced by 500 r whole body x-irradiation in weight, amount of tissue water, and weight of the contents of the stomach, small intestine and large intestine, were studied in male Sherman strain rats, weighing between 150 to 200 g. Ten animals were sacrificed daily on the 1st, 2nd, 3rd, 4th, 5th and 7th post-irradiation days. Thirteen comparable, unirradiated animals served as controls. Animals were irradiated in aluminum cages, 3 to a cage, and placed above a standard 50 cm therapy cone, such that the beam passed anterior-posteriorly. Radiation factors were: 200 kv.p; 25 ma; cone size, 20 x 20 cm; H. V. L., 0.82 mm cu; filters, .25 mm cu 1 mm al; backscatter material, .75 cm masonite; target to skin distance, 50 cm; dose rate, 44.0 r per minute (500 r was approximately an LD_{30}—30 days). Body weights were recorded before and at intervals after irradiation. Data on body weights were combined with data from a previous experiment(7) using similar animals under identical radiation conditions (total of 82 animals). Determinations of weights of organs, of gastrointestinal contents, and water content of tissues, were made in the following manner: The animals were killed by a blow on the head at approximately the same time each day. (Since the rat is a nocturnal feeder they were killed in the morning in order that the gastrointestinal contents would be more comparable.) The gastrointestinal tract was stripped free of mesentery and removed at the esophageal-cardiac and ano-rectal junctions. The gastrointestinal tract was then

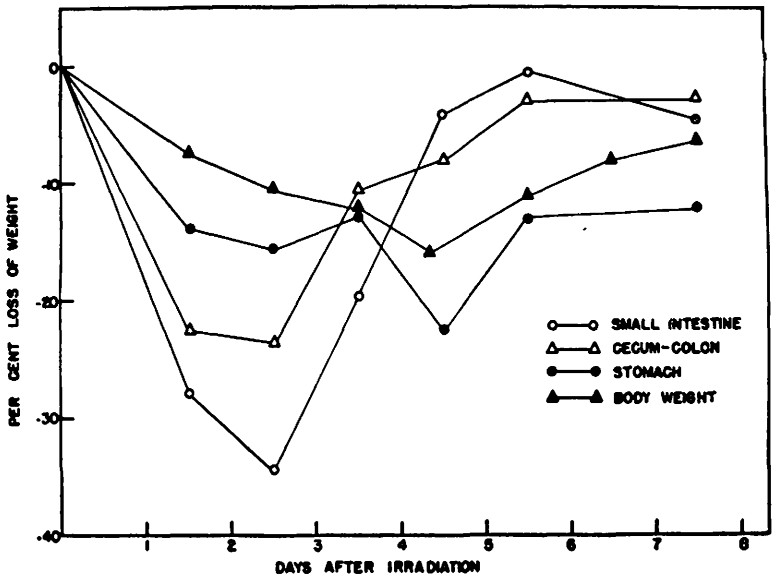

FIG. 1. Effect of 500 r X-irradiation on weights of components of gastrointestinal tract of the rat.

separated into 3 components, the stomach, the small intestine, and large intestine (cecum-colon), by severing at the pyloric sphincter and ileocecal junctions, respectively. Each component with contents was then weighed. The parts were cleaned thoroughly with water, blotted free of excess moisture and wet weights were obtained. The parts were then dried in a 100°C oven for 18 hours. (This proved to be adequate to achieve constant weight.) Water content was expressed as per cent wet weight. The mean of these values for each category was compared to the unirradiated control mean values.

Results and discussion. The changes in weight of the 3 parts of the gastrointestinal tract of the rat following 500 r x-irradiation are shown in Table I and represented graphically in Fig. 1. Although all 3 components showed depressed weight during the first 4 days after irradiation, the small intestine showed considerably greater weight loss than did the stomach or large intestine.† It is believed this greater weight loss of the small intestine reflects its greater sensitivity to radiation. Though the small and large intestines returned to approximately normal weight by the 4th and 5th days, it is interesting that the weight of the stomach did not return to normal during the course of the experiment.

Body weight loss was not nearly so extreme as gastrointestinal weight loss (Fig. 1). Following irradiation, the animals showed a steady loss of weight, reaching 16% below pre-irradiation weight on the 4th day. This was followed by a slow gain in weight, pre-irradiation weight being attained by the 11th day. Body weight changes during the early post-irradiation period might have been largely a reflection of the state of the gastrointestinal tract. Smith(8) and Nims *et al.*(9) showed that irradiated starved rats lost the same body weight as starved rats without irradiation. In irradiated rats that had access to food, however, changes in weight occurred which were dose dependent (up to 600 r) (9). The weight changes were probably related in part to the degree of anorexia with resulting lowered food intake. The anorexia was probably largely a reflection of the degree of damage of the gastrointestinal tract.

The etiology of the acute changes in weight of the components of the gastrointestinal tract are no doubt quite complicated. The variations in weights were not due to changes in water content (edema or dehydration) of these tissues since the water content remained

† $P < 0.01$ by t-test on 2nd day.

fairly constant throughout the period of observation, with no marked variation from the controls. The variation in mean per cent water of the tissues was as follows: stomach, controls, 77.7; irradiated, 77.0-78.1 (mean 77.5); small intestine, controls, 79.7; irradiated, 79.2-80.6 (mean 79.4); large intestine, controls, 79.9; irradiated, 79.2-81.0 (mean 80.1).

Reduced food intake occurring during the first few days would not likely account for all of the weight loss. In a previous experiment (7) it was shown that in rats starved to lose the same body weight as irradiated rats, the small intestine did not show as great a weight loss as did the small intestines of the irradiated animals. Therefore, aside from nutritional effects, some of the weight loss must be accounted for on the basis of specific changes induced by irradiation. No doubt much of the weight loss may be accounted for on the basis of destruction and failure of normal replacement of the sensitive epithelial and lymphoid cells. Epithelial cell destruction occurred primarily during the first 24 hours with this dose of radiation(7). Leblond and Stevens(10) have shown that the intestinal epithelium normally replaces itself about every 1½ days. Since radiation produces mitotic inhibition of these epithelial cells(11-13), failure of normal replacement of the epithelium becomes an important factor in weight loss.

The contents of the gastrointestinal tract showed considerable variation during the 7-day post-irradiation period (Table I). The marked increase in contents of the stomach during the first 3-4 days demonstrated clearly the radiation-induced emptying defect of the stomach, which has previously been reported (14-16). Increased tone of the pyloric sphincter together with the atony of the stomach might well have accounted for this condition. During the 3-4 day period the contents of the small and large intestines became decreased slightly and liquid and foul-smelling in nature. These changes coincided with the time when the gross appearance of the intestine was worst, *e.g.* atony, dilatation and lack of motility.

By the 4th-5th days, the contents of the entire gastrointestinal tract assumed a normal, semisolid state. The increased contents noted during this time probably represented increased food intake to compensate for the earlier period of lowered food intake. At this time, also, the weight of the gastrointestinal tract and the gross appearance returned toward normal.

The acute fluctuations of weight and contents of the gastrointestinal tract were part of an over all complicated reaction of that system to radiation that occurred during the early post-irradiation period. Thus, after 500 r in the rat the first 3-4 days were characterized by morphological and functional changes associated with the gastrointestinal tract, among which were: damage to the epithelial and lymphoid elements; loss of weight of the gastrointestinal tract, particularly of the small intestine; a short-lived increased intestinal motility followed by depressed motility; reduction in activity of the enzyme cholinesterase(7); anorexia with lowered food intake and loss of body weight; and the development of abnormal liquid contents of the intestine with diarrhea (in some animals). The period from the 3rd and 4th day to the 7th day was marked by recovery which began rather abruptly about the 3rd or 4th post-irradiation day. There was no further evidence of epithelial damage, gastrointestinal weights returned nearly to normal, motility appeared normal, the enzyme cholinesterase was slowly increasing, the animals began to eat normally and to gain weight, diarrhea disappeared and the contents became normal in appearance.

The gastrointestinal changes reported in this paper apply to the 500 r x-ray dosage used under the conditions of this experiment. Many of the phenomena are dose dependent, *e.g.*, intestinal weight loss(17). With larger doses many of the symptoms and signs may be aggravated and with smaller doses they may be less prominent.

Summary. 1. The effect of 500 r whole body irradiation on organ weights and weights of the contents of the stomach, small intestine and large intestine of the rat was studied. All three components showed loss of weight during the first 3- to 4-day post-irradiation period which was greater than body weight loss. The stomach, small intestine and large intestine

showed percentage weight losses of 15.7, 34.4 and 23.6, respectively. Organ weights, except for the stomach, returned nearly to normal on the 4th and 5th day. The significantly greater weight loss in the small intestine was believed to reflect greater sensitivity of this part to ionizing radiation. It was pointed out that these weight changes were not due to dehydration or edema of the tissues or to the lowered food intake alone, but were in a large part due to specific effects of radiation. 2. The stomach showed the greatest variation in contents after irradiation, with a marked increase occurring during the first 72 hours which was believed to be associated with delayed emptying of the stomach. During this same period the small intestine and large intestine showed slightly reduced contents which became liquid and foul-smelling in character. From the 3rd to 4th days through the 7th day there was a marked increase in contents in all parts above the control range with a change to the normal semi-solid state. It was believed that this change was the reflection of compensatory increased food consumption associated with improved gastrointestinal function.

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Certain Nucleotide Relationships in Normal and in Tumor-Bearing Mice.* (20110)

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We have reported that male mice bearing implanted sarcoma 180 undergo a significant lowering in blood adenosine triphosphate during the interval of tumor growth(1). The first part of the present investigation was concerned with ascertaining whether similar alterations in blood nucleotide appear in female mice during the estrous period as compared with the diestrous, or during pregnancy when extensive mitotic activity occurs which may be similar to that of tumor growth. At the same time, analyses were performed on the blood of

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