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ALTERATION OF INTESTINAL VASOACTIVITY DURING THE DEVELOPMENT OF THE GASTROINTESTINAL RADIATION SYNDROME

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ARMED FORCES RADIOBIOLOGY RESEARCH INSTITUTE
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Bethesda, Maryland

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ALTERATION OF INTESTINAL VASOACTIVITY DURING THE DEVELOPMENT OF THE GASTROINTESTINAL RADIATION SYNDROME

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FOREWORD
(Nontechnical summary)

The terminal phase of the gastrointestinal radiation syndrome ends in the collapse of the blood circulation. This clinical picture resembles in many aspects shock induced by injury, hemorrhage, dehydration, etc. The initiating and maintaining deteriorating factor due to ionizing radiation injury (at the dose level of 1500 rads whole-body gamma-neutron radiation used in this study) is unquestionably the structural breakdown of the small intestine. However, there is a lack of understanding about those factors which modify and eventually cause irreversible clinical deterioration. One of these suspected factors might be the disproportionately increased constriction of blood vessels to the small intestine with a subsequent persistent low intestinal blood flow state. Indeed, prolonged low intestinal blood flow itself can cause shock and lethality.

In this study, the intestinal vasoactivity of blood vessel function and structure during the postirradiation period was investigated. The resistance vessels of the dog small intestine were challenged by sudden and gradual changes in blood pressure. There were indications that during the development of the gastrointestinal radiation syndrome the functional capacity of the intestinal blood vessels is altered. It seems justified to say that this altered integrity of the intestinal vasomotion could be the key factor inducing cardiovascular collapse

ABSTRACT

The functional vascular integrity of the small intestine in relationship to its morphological alterations during the postirradiation period was examined. Dogs were exposed to 1500 rads (midline tissue dose) of mixed gamma-neutron radiation. Hemodynamic parameters of an in situ intestinal loop were measured in response to the systemic administration of norepinephrine, isoproterenol and gradual bleeding and reinfusion. The results indicate that 48 hours postirradiation when the capillaries are virtually intact and the systemic hemodynamic parameters are not altered yet, the functional integrity of the intestinal vasculature is already significantly deteriorated. The intestinal resistance vessels of the irradiated animals did not exert "autoregulatory escape" as the controls did. After 72 hours the vasocompensation to the sudden blood pressure changes was also markedly changed. The fluctuation of the intestinal resistance values during the bleeding and reinfusion periods demonstrated neurohumoral imbalance in the postirradiation period. On the basis of these results it is postulated that the terminal cardiovascular collapse in irradiated animals might be due to the development of intestinal ischemic shock.

I. INTRODUCTION

One of the hemodynamic features in the terminal phase of the gastrointestinal radiation syndrome is the impairment of the small intestinal blood flow.[9,10] This alteration is due to the disproportionately increased intestinal vasoconstriction commonly observed in states of hemodynamic deterioration leading to ischemia. The significance of this observation is enhanced by the fact that development of small intestinal ischemia has been connected with the irreversibility of different types of shock.[1,7,15] Although in the early part of the postirradiation period apparently the systemic hemodynamic homeostasis is still maintained,[1] nevertheless some factors which might participate in the intestinal blood vessels' tone are already altered.

There is a general agreement that the radiation-induced loss of the epithelial layer of the small intestine is responsible for the initiation and continuation[8,14] of the deteriorating sequence through impaired absorption, dehydration, electrolyte imbalance, etc. However, considerable controversy exists about the contribution of the altered intestinal vasomotion which induces the cardiovascular collapse and eventually leads to the terminal phase of the radiation injury.

In order to measure the intestinal vasoactivity and the functional capacity of the small intestinal circulation during the development of the gastrointestinal syndrome, an in situ dog intestinal loop preparation was chosen as the experimental model. First, the small intestinal resistance vessels were challenged by alpha and beta adrenergic agents in an attempt to alter immediately the intestinal pressure-flow relationship. Then, the intestinal blood vessels were exposed to gradual hemodynamic alterations by applying controlled blood withdrawal and reinfusion.

II. MATERIALS AND METHODS

Eighteen male beagles, 12 - 14 months old and weighing 9.5 - 11.5 kg were used in this study. The animals were divided into three groups: irradiated, with 48- and 72-hour postirradiation periods, and nonirradiated controls. Food was withheld from the dogs overnight before irradiation. Water was available ad libitum. At approximately 1 hour before irradiation the animals were placed in Lucite restraining cages and transferred to the exposure room of the AFRRI-TRIGA reactor where they received 1500 rads midline tissue dose of pulsed mixed gamma-neutron radiation. The AFRRI-TRIGA reactor and the exposure room have been described previously.[2] The methods as delineated by Pitchford and Thorp[16] were used for dosimetry. The irradiated animals were subjected to the experimental procedures described below at 48 and 72 hours postirradiation. All animals were free to consume food and water ad libitum before the experimental procedure.

Anesthesia was induced by intravenous administration of 30 mg/kg sodium pentobarbital (Nembutal). After insertion of a tracheal tube, the abdomen was opened at the midline. Figure 1 shows the experimental setup. A section of the jejunal part of the intestine, usually weighing about 12 - 15 grams, was chosen for the experiment. The mesenteric vein draining the intestinal segment was cannulated with a heparinized polyethylene tubing (Clay-Adams PE-320 i.d. 0.106", o.d. 0.138") and the venous outflow was registered by an electronic drop counter. The venous blood was collected in a beaker and its volume was controlled by an electronic leveler which turned on a peristaltic pump (Harvard Apparatus 1215) to return the blood to the animal via the right femoral vein when the preset volume of 15 ml was reached. The beaker originally

contained 15 ml of heparinized saline solution in a total dose of 5000 units. The venous outflow pressure was set continuously at zero. The wide cannula inserted into the mesenteric vein was always introduced far enough distally so that it was well inside the sealed opening thereby avoiding collapse of the vein by undue lateral pressure. A small mesenteric arterial side branch near the intestine was catheterized by a heparinized cannula (polyethylene tubing, Clay-Adams PE-50 i.d. 0.023", o.d. 0.038") and the arterial inflow pressure to the intestine was measured by a Statham pressure transducer (Model No. P23Db). During the surgical procedures great care was taken to leave the vessels and the nerves intact.

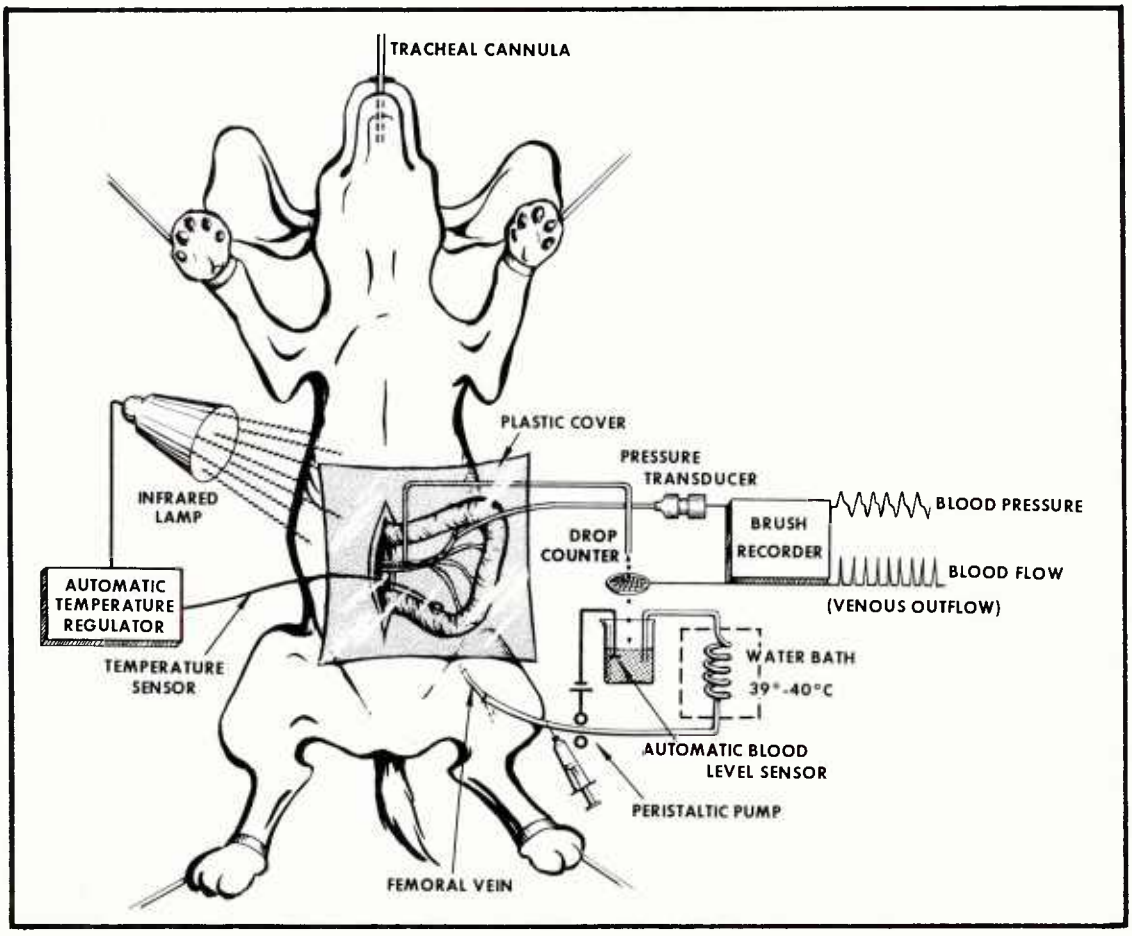

Figure 1. Experimental setup

Drying and cooling of the exposed parts of the intestine were avoided by covering them with a wet gauze and a plastic sheet which also allowed visual observation. The temperature was kept at 38°C with the aid of an infrared lamp connected through an automatic thermoregulator to a temperature sensor. The temperature of the animal was also maintained constant at 37.5°C with a heating pad.

The experimental procedures began 1 hour after anesthesia or about 30 minutes (base-line period) after completion of the surgical procedure. The following parameters were obtained (or calculated) and continuously recorded by an electronic recording system (Brush Instruments Division, Cleveland, Ohio): (1) intestinal mean arterial pressure (calculated from the diastolic blood pressure + 1/3 pulse pressure); (2) blood flow (venous outflow of the intestinal segment calculated as milliliters per minute per 100 g of intestine after excising and weighing the intestinal loop at the termination of the experiment; the mesenteric tissue was trimmed from the intestinal segments before weighing them); (3) intestinal resistance (expressed in peripheral resistance units as the ratio of the mean arterial pressure in millimeters of mercury and the blood flow in milliliters per minute per 100 g of intestine); and (4) heart rate. Histological sections of the jejunum were stained with hematoxylin-eosin. For capillary preparations, the Microfil technique (Canton Bio-Medical Products, Swarthmore, Pennsylvania) was used.

The experimental protocol consisted of the following procedures. To cause vasoconstriction an alpha adrenergic agent, norepinephrine (5 μg/kg), was injected intravenously and its direct and indirect hemodynamic effects on the intestinal segment were registered and calculated. After 10 minutes, maximal intestinal vasodilation was

induced by intravenous administration of 5 mg/kg of isoproterenol hydrochloride as a beta adrenergic agent and the intestinal hemodynamic responses were monitored again for a 10-minute period. Both drugs were obtained from Winthrop Laboratories, New York, N. Y.

In the second part of the experiment, the animals were bled at the rate of 40 ml/min until 200 ml of total volume (about 25 percent of the total blood volume) were removed. When this was achieved, the blood was reinfused immediately at the same flow rate. The rate of bleeding and reinfusion was controlled by a Harvard peristaltic pump connected to the femoral vein. While the animals were bled or reinfused the aforementioned hemodynamic parameters were recorded.

Statistical analysis of the data obtained in this study was performed utilizing a Scientific Data Systems 920 digital computer. This computer was programmed to calculate means, standard deviations and correlation coefficients by the least squares method and to perform a paired t-test analysis.

III. RESULTS

In the first part of the experiment the hemodynamic alterations of an in situ jejunal loop after single intravenous injections of the alpha and beta adrenergic agents were recorded. In Figure 2, the postinjection time sequence in 1-minute intervals for the mesenteric arterial pressure, the intestinal blood flow (venous outflow from the jejunal loop), intestinal resistance, and the heart rate changes are plotted.

There were no significant differences in the mean arterial pressure of irradiated and nonirradiated animals either initially or postinjection (Figure 2A). The initial venous outflows of the intact and 48-hour postirradiation intestinal loops were still in

the same range, however the blood flow values at 72 hours postirradiation decreased significantly (Figure 2B). After norepinephrine injection the sudden systemic blood pressure change resulted in a transient increased intestinal blood flow in all groups. Thereafter, the alpha adrenergic effect was manifested in a significantly sharp decline in the intestinal blood flow in all groups with the largest response in the 48-hour post-irradiation group. The beta adrenergic agent (isoproterenol) caused an approximately

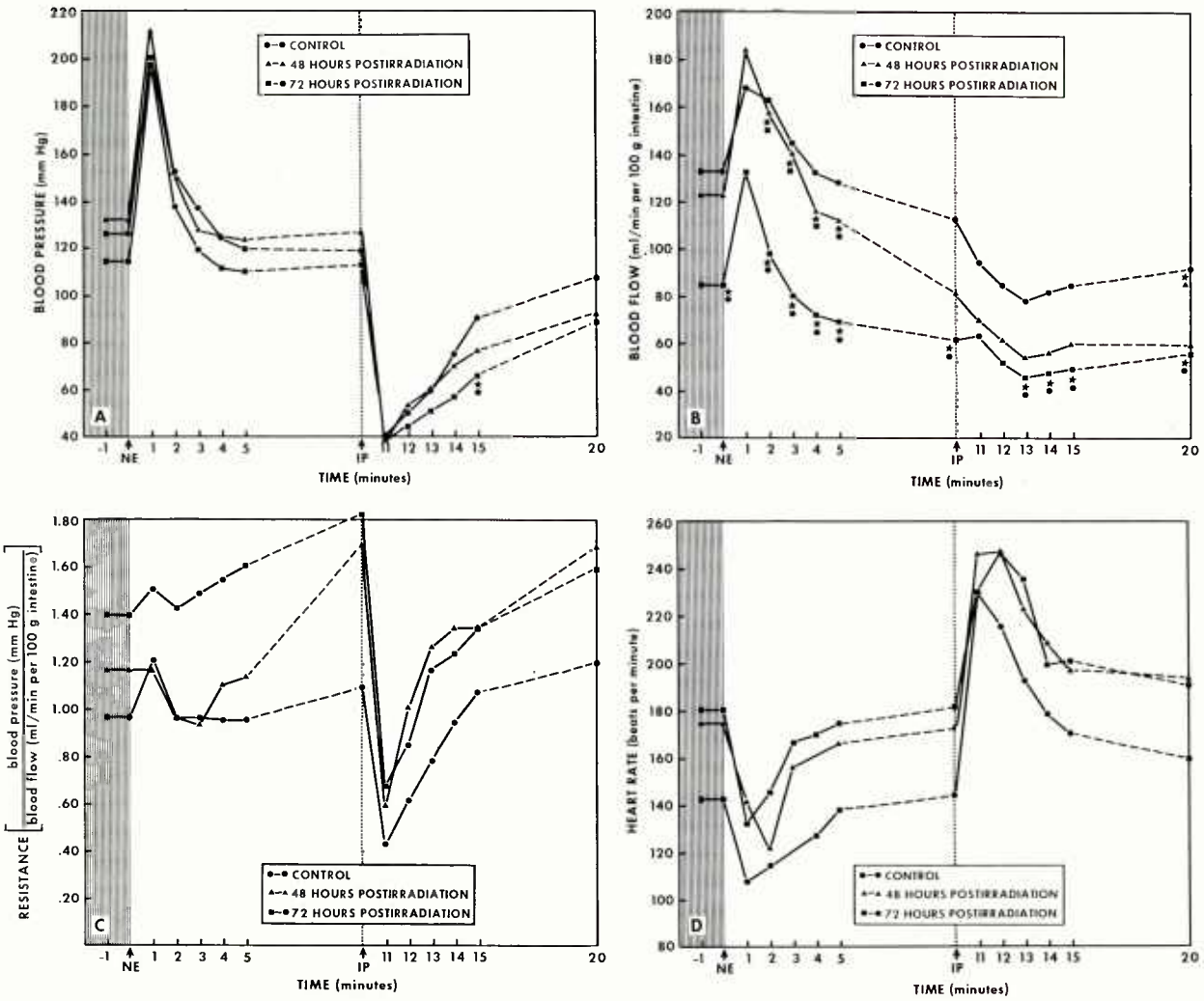

Figure 2. Changes in minute intervals after injections of norepinephrine (NE) and isoproterenol (IP). (A) Blood pressure changes; (B) Intestinal blood flow changes; (C) Intestinal vascular resistance changes; (D) Heart rate changes. ★ indicates significant difference ($p < 0.01$).

30 percent decline of the intestinal blood flow in all groups within the first 3 minutes postinjection time. Thereafter, it increased steadily without returning to the original preinjection values.

The initial peripheral resistance values of the intestinal loops in the irradiated animals were higher than those of the normal controls (Figure 2C). After norepinephrine injection the control peripheral resistance balanced out within 2 minutes and remained stable contrary to that of the irradiated animals where the resistance continued to rise. However, even at these increased intestinal resistance values, the response to isoproterenol to reach maximum vasodilation appeared to be the same in all groups. Furthermore, the immediate change after 1 minute postinjection also showed the same steep slope of response.

The heart rate curves (Figure 2D) showed the characteristic responses to the adrenergic agents. Compensatory vagal reflex activity slowed the heart, overcoming the direct cardiac accelerator action of norepinephrine. The direct chronotropic action of isoproterenol was also well expressed in all groups. Although the irradiated animals' initial response average values were higher than the normal controls percentagewise (taking the initial values as 100 percent), the magnitude of the chronotropic responses in all groups was similar.

When blood pressure was plotted against intestinal blood flow it was possible to gain a better insight into the intestinal vasoactivity induced by the two adrenergic agents. In Figure 3 the percent change of the average blood pressure was plotted against flow changes, grouped at minute intervals. It is important to point out that both adrenergic agents first altered the intestinal blood flow immediately by a sudden

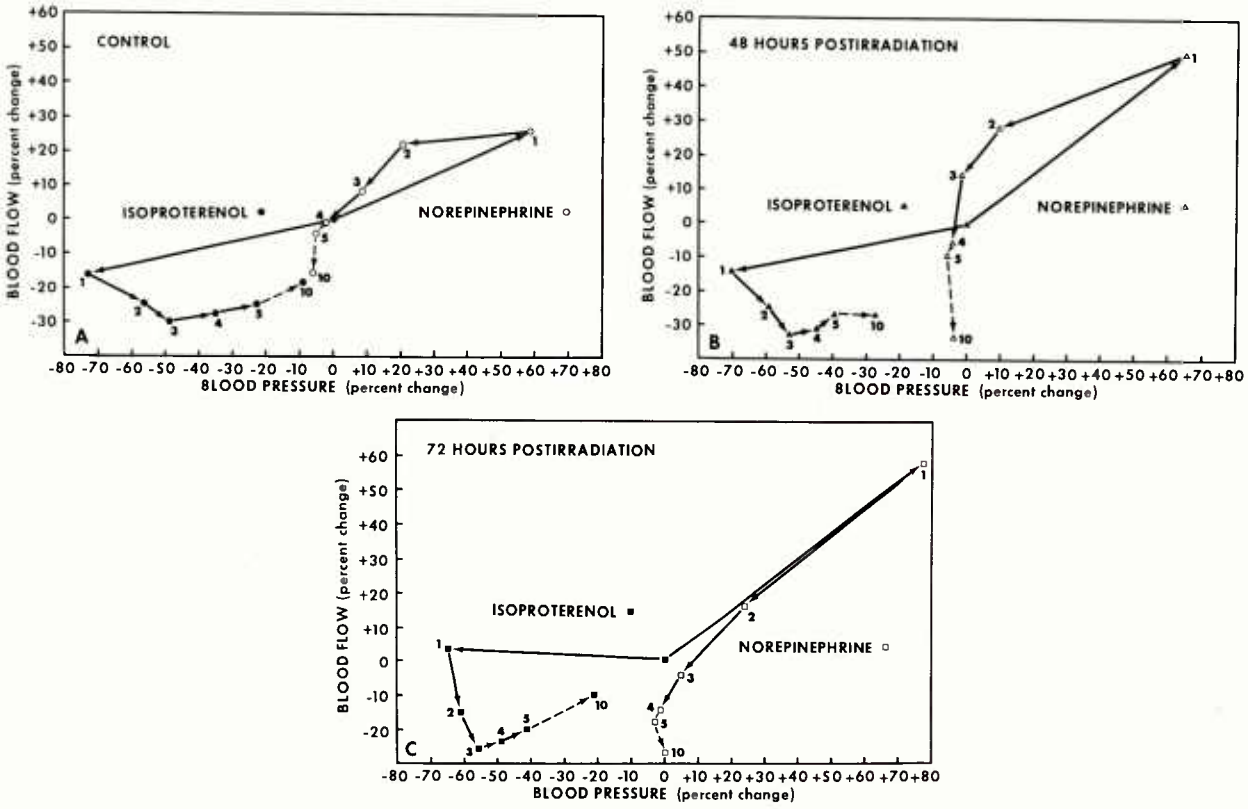

Figure 3. Intestinal blood flow and blood pressure changes expressed in percentage of the preinjection values (before norepinephrine and isoproterenol, respectively). Each point represents the average of minute intervals during the postinjection period.

change of systemic blood pressure and only thereafter their local effects were manifested. The intestinal vessels of the intact and 48-hour postirradiation groups showed a gradual response after the first minute (Figure 3A, B) however the slope of the increased blood pressure to blood flow ratio of the 72-hour postirradiated intestines was followed immediately by a similar slope in the opposite direction without any compensation (Figure 3C). When the so-called vasoactive compensation for the first 2 minutes norepinephrine postinjection time was calculated, the values listed in Table I were obtained by using the following formula:

$$\text{vasoactive compensation} = \frac{(A-R)}{A} \times 100$$

where A (action) and R (reaction) of the intestinal blood flow changes (in percentage of the initial blood flow) were calculated for 100 mm Hg blood pressure change.

Table I. Percentage Vasoactive Compensation of the Intestinal Resistance Vessels after the Administration of Norepinephrine

Groups	Time intervals (min)	Change in blood pressure (mm Hg)	Change in blood flow (percent)	Percent blood flow change per 100 mm Hg blood pressure change	Vasoactive compensation (percent)
Control	0 - 1	+ 74.6	+ 26.4	+ 35.39	+ 75.2
	1 - 2	- 47.8	- 4.2	- 8.78	
48 hours postirradiation	0 - 1	+ 80.2	+ 50.0	+ 62.34	+ 42.4
	1 - 2	- 60.2	- 21.6	- 35.88	
72 hours postirradiation	0 - 1	+ 83.0	+ 57.4	+ 69.16	- 0.10
	1 - 2	- 59.3	- 41.3	- 69.65	

When the bleeding part of the experiment was started the slope of the blood pressure to blood flow regression lines of the irradiated animals (Figure 4A) was shifted significantly down to the vasoconstrictor side compared with the control. At these lower levels, the induced intestinal blood flow changes by the gradual decrease of blood pressure were similar or even somewhat better (less steep slope) than in the intact, nonirradiated animals. However, it is important to note that the control intestinal vessels showed reactive hyperemia during reinfusion which was completely missing in the irradiated intestinal resistance vessels (Figure 4B). When the intestinal peripheral resistance percentage changes were plotted against the blood pressure changes (Figure 5) during the blood withdrawal (Figure 5A) and reinfusion (Figure 5B) periods, it became clear that the intestinal blood vessels of the irradiated animals

demonstrated a considerable fluctuating vasoactivity, indicating a less coordinated vascular regulatory process. The fluctuation of the intestinal peripheral resistance was more apparent in the earlier postirradiation period, at 48 hours.

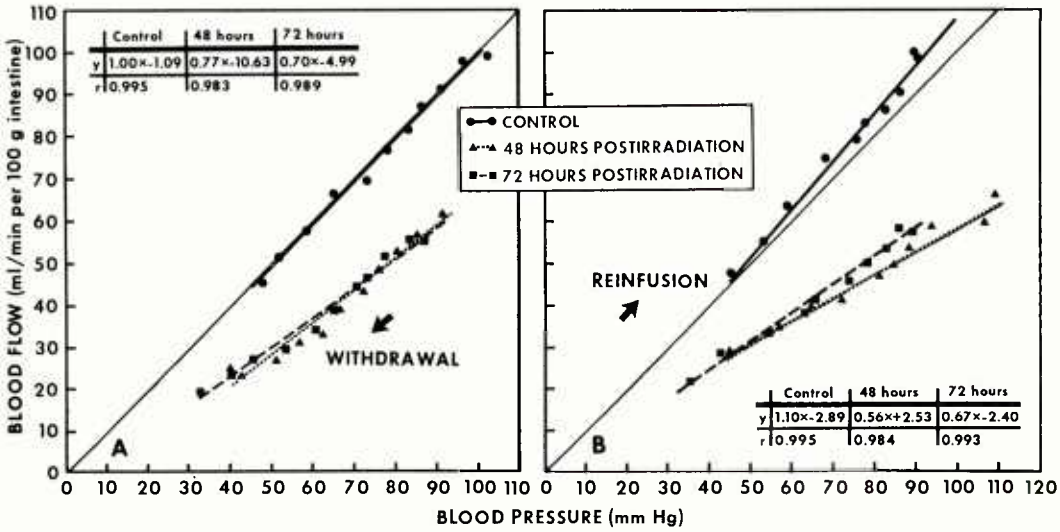

Figure 4. Intestinal blood flow and blood pressure changes during gradual blood withdrawal and reinfusion. Each point represents the average changes induced by subsequent 20-ml blood withdrawal or reinfusion. Diagonal line depicts an unchanged intestinal resistance; peripheral resistance unit is 1. Points above or under the line correspond to vasodilation or vasoconstriction, respectively.

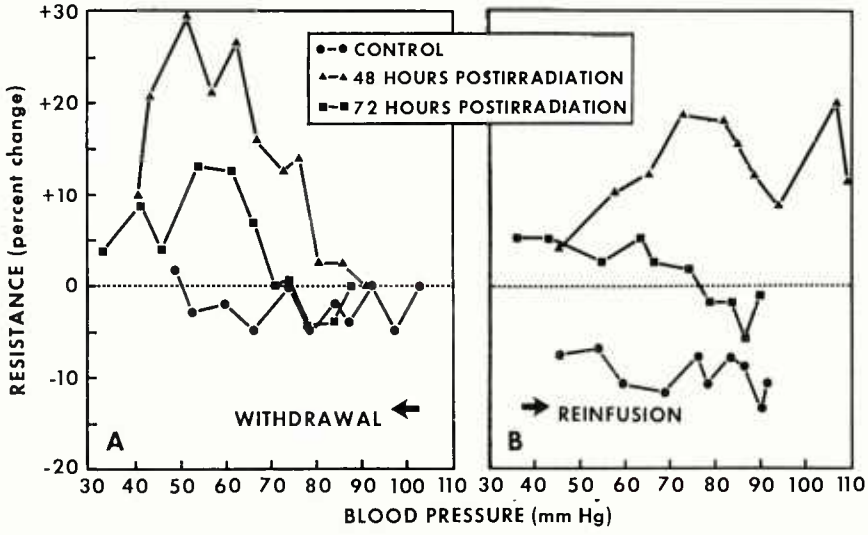

Figure 5. Intestinal vascular resistance changes in percentage of the prehemorrhagic values according to the blood pressure alterations during gradual blood withdrawal and reinfusion periods. Each point represents the average percent change of the intestinal resistance induced by subsequent 20-ml blood volume alterations.

IV. DISCUSSION

In the present study, experiments were performed on intestinal segments which were not separated, had intact vasoconstrictor fibers and vagal innervation. Furthermore, to avoid metabolic shifting, the animals were not starved. Since the venous outflow pressure was set at zero, it is justifiable to say that the intestinal resistance was caused by the resistance vessels beginning morphologically at the arterioles and extending to the precapillary sphincters.

The present study is concerned with the functional capacity of the irradiated intestinal resistance vessels to respond when they are challenged by rapid or gradual alterations of the arterial blood pressure. In the first case apparently the reflexly mediated regulatory processes are involved. Sarnoff and Yamada[17] described potent baroreceptors in the mesenteric vasculature. The pressure alterations cause activation of afferent nerve impulses from these baroreceptors with a resultant negative feedback effect. Maťorova[12] reported that irradiation can produce an inhibition or total reduction of the biopotentials (nerve conductivity).

Therefore, the possibility exists that the nerve conductance disturbance was manifested at 72 hours postirradiation when the intestinal resistance vessels appeared to be passively altered by the abrupt change of the arterial pressure.

Wallentin[19] demonstrated that the vasoconstrictor fiber effect on the intestinal capillary resistance vessels is strongly counteracted by a local vasodilator mechanism. This causes an "autoregulatory escape" from the constrictor fiber influence, so balanced that in the steady-state phase of constrictor fiber activity the intestinal flow resistance is only modestly increased. Shehadeh et al.[18] confirmed this

phenomenon with prolonged interarterial infusion of vasoactive drugs. The present data concerning the normal, control animals substantiate these observations. However, in the irradiated animals this so-called "autoregulatory escape" was not manifested after norepinephrine injection. The intestinal resistance continuously increased during the postinjection period with a concomitantly decreasing intestinal blood flow.

During the postirradiation period the increased resistance in the intestinal vessels (down to the precapillary sphincters) due to sympathetic activity or vasoactive agents might render ineffective the autonomous microcirculatory regulation of pressure and flow patterns within the exchange vessels. This phenomenon is not a specific hemodynamic feature of the gastrointestinal radiation syndrome since it certainly can be observed in different pathological states. It is well known however that the irradiated animals' blood vessels develop extreme reactivity to constrictor stimuli.[11]

It was reported that in the dog and cat little or no increase in mesenteric resistance is usually seen following hemorrhage.[5] The present data confirm this observation when in the second phase of the study the intestinal vasculature was exposed to gradual hemodynamic changes. During the blood withdrawal and reinfusion periods only a fine oscillation appeared in the resistance of the normal intestinal vessels. However, the vasomotor regulatory processes of the irradiated vessels show a marked fluctuation during the hemodynamic adaptation.

Zweifach[21] and Windmueller et al.[20] indicate that the intestinal blood flow depends on the well organized local metabolic and/or some of the circulating humoral factors. A general change in the content of epinephrine and norepinephrine of various tissues was recently reported in irradiated animals.[13]

Goodall and Long[6] showed that the physiological demand for epinephrine and norepinephrine is so great after irradiation that the adrenal gland is partially or completely depleted of its catecholamine; however, the biosynthesis of these hormones does not decrease; if anything, it increases. Similar observations were made about the adrenal cortex[4] concerning production of glucocorticoids. Furthermore, Zweifach and Kivy-Rosenberg[22] indicated that after whole-body irradiation, responses of terminal arterioles and precapillaries to epinephrine and norepinephrine are exaggerated.

The present data concerning the fluctuating intestinal resistance values when gradual blood withdrawal and reinfusion were performed substantiate the existence of the neurohumoral imbalance during the postirradiation period.

During blood reinfusion in control dogs there was a proportionately higher increase in the blood flow compared with the blood pressure increase (reactive hyperemia). This phenomenon was completely missing in the irradiated intestinal vessels. Instead, their tone was steadily shifted to the vasoconstriction side. It is necessary to point out, however, that during the development of the gastrointestinal syndrome the increased peripheral resistance has two other but less significant components; namely, increased viscosity and the formation of plugs in the capillaries (cell debris), besides active vasoconstriction.

Everhard et al.[3] showed recently that decreased intestinal blood flow leads to a progressive vasoconstriction with a persistent refractory intestinal ischemia. This process, the altered integration of the intestinal vasomotion, might be one of the determinant factors in the syndrome. The progressive alterations of the hemodynamic regulation lead to hypotension, intestinal ischemia and the terminal cardiovascular

collapse, regardless of whether the electrolyte and water balance is maintained. Therefore, it seems justifiable to conclude that the terminal phase of the gastrointestinal radiation syndrome resembles the pattern of intestinal ischemic shock.

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13. ABSTRACT

The functional vascular integrity of the small intestine in relationship to its morphological alterations during the postirradiation period was examined. Dogs were exposed to 1500 rads (midline tissue dose) of mixed gamma-neutron radiation. Hemodynamic parameters of an in situ intestinal loop were measured in response to the systemic administration of norepinephrine, isoproterenol and gradual bleeding and reinfusion. The results indicate that 48 hours postirradiation when the capillaries are virtually intact and the systemic hemodynamic parameters are not altered yet, the functional integrity of the intestinal vasculature is already significantly deteriorated. The intestinal resistance vessels of the irradiated animals did not exert "autoregulatory escape" as the controls did. After 72 hours the vasocompensation to the sudden blood pressure changes was also markedly changed. The fluctuation of the intestinal resistance values during the bleeding and reinfusion periods demonstrated neurohumoral imbalance in the postirradiation period. On the basis of these results it is postulated that the terminal cardiovascular collapse in irradiated animals might be due to the development of intestinal ischemic shock.

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