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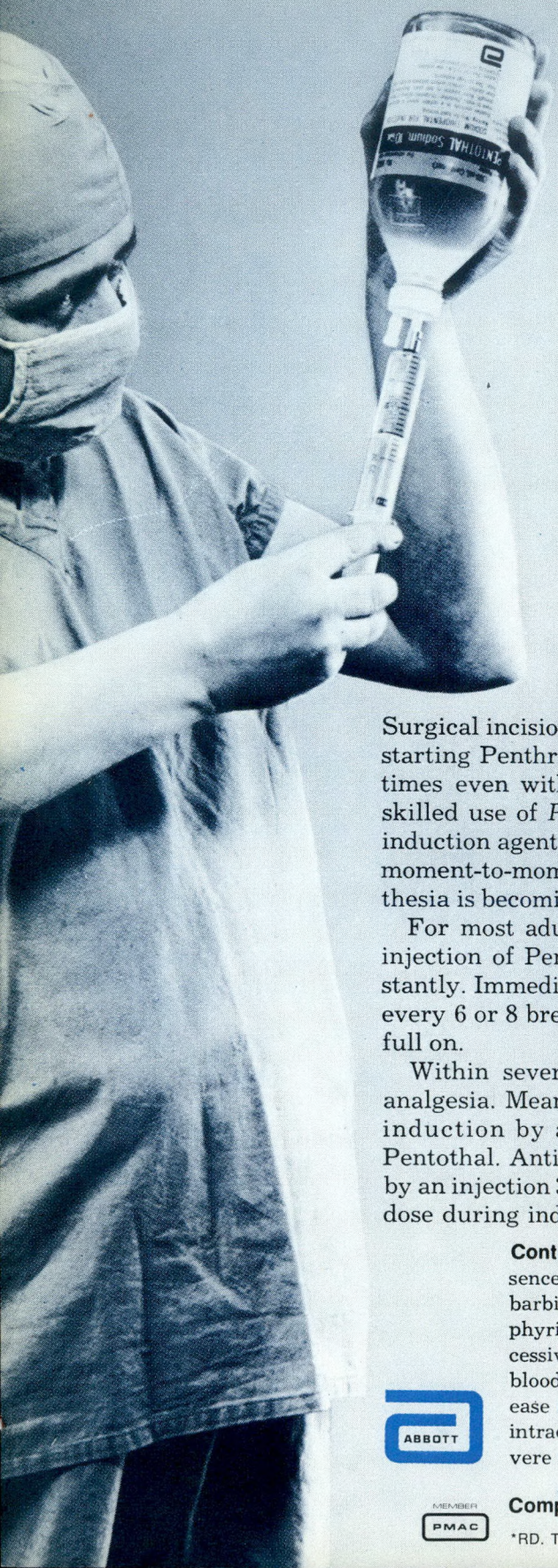

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Surgical incision can get under way surprisingly soon after starting Penthrane—usually in less than 5 minutes. Sometimes even within 2 or 3 minutes. The secret is in your skilled use of *Pentothal*. Proper amounts of this versatile induction agent can provide the smooth, rapid narcosis and moment-to-moment control needed while Penthrane anesthesia is becoming established.

For most adults, start induction with a 160 to 200 mg. injection of Pentothal. Unconsciousness occurs almost instantly. Immediately introduce 0.5% Penthrane in N_2O-O_2; every 6 or 8 breaths open the vaporizer another 0.5% until full on.

Within several minutes Penthrane produces profound analgesia. Meanwhile, control any patient reaction during induction by additional 40 to 100 mg. increments of Pentothal. Anticipate and prevent response to the incision by an injection 30 to 60 seconds beforehand. Total Pentothal dose during induction rarely need exceed 500 mg.

Contraindications, precautions—Contraindicated in absence of suitable veins, allergy or hypersensitivity to barbiturates, status asthmaticus, latent or manifest porphyria. Use special care in presence of hypotension, excessive premedication, hepatic dysfunction, increased blood urea, severe anemia, or severe cardiovascular disease (including peripheral circulatory failure, increased intracranial pressure, asthma, myasthenia gravis, severe uremia). Have resuscitative equipment present.

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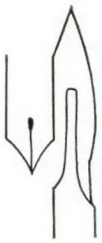

QUILL ON SCALPEL This section provides a medium through which Canadian surgeons can declare themselves, briefly and informally, on the day-to-day affairs of surgery.

VASOACTIVE DRUGS IN SHOCK: THE GREAT DISILLUSION

Thirty years of intensive laboratory and clinical research into the value of vasoactive drugs in the management of shock have failed to fulfil the bright promises of the 1950's and 1960's. After much enthusiasm for the vasoconstrictors, the attention has shifted to the vasodilators. By now, a number of α and β stimulators as well as α and β blockers have been tried but they do not appear to improve our patients' chances for survival. As an example of this new awareness, Shoemaker and Brown[1] have recently summarized their detailed clinical studies on the sequential use of drugs in various types of shock. They report that none of the commonly recommended vasodilators and vasoconstrictors improve the clinical and hemodynamic course of shock patients. The only apparent exception is isoproterenol, which is a comparatively weak vasodilator and may help some patients through its strong cardiotonic action. Unfortunately, we also know that an increased cardiac output in shock is not necessarily followed by a better oxygen consumption or a better survival. Such sobering reports are bound to have far-reaching implications because entire careers, laboratories and university departments have been built around a favourite shock theory and its related set of vasoactive drugs.

Obviously such efforts have not been entirely wasted because they have taught us something about the physiology of shock, but the time has come to ask whether the "vasoactive approach" to the management of these patients does not, after all, rest on a false hypothesis: the basic premise was that since shock was the manifestation of a failure of tissue perfusion, the striking vascular phenomena seen in this condition constituted the disease itself. Consequently, it all became a matter of whether the wrong blood vessels opened too little or too much, at the wrong place or at the wrong time. And for each theory, an appropriate drug was proposed as the ultimate answer.

The underlying fact that many failed to appreciate is that the vascular changes seen in shock may simply represent the best possible balance between the respective priorities of pressure and flow under the circumstances imposed on the vascular system. Such circumstances include reduction in circulating blood volume, changes in blood composition, increased metabolic requirements and heart failure. We should then concentrate on dealing with organ failure and correcting deficit where it exists rather than tampering with a probably flawless homeostatic response. Let us remember the principle laid down in the last century by Claude Bernard: the body does not make mistakes of homeostasis when attempting to preserve the integrity of the *milieu intérieur*. When examining specific vascular changes taking place in shock we must decide early whether such changes constitute a crucial anomaly or simply the most desirable response to a given assault.

As for all the solutions of vasoactive wonder drugs with which we have infused our dying patients, they must surely go down in history as unexpected varieties of embalming fluid.

BERNARD J. PEREY

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REFERENCE

1. SHOEMAKER WC, BROWN RS: Dilemma of vasopressors and vasodilators in therapy of shock. *Surg Gynec Obstet* 132: 51, 1971

OPEN LETTER FROM A UNIVERSITY GENERAL SURGEON

Dear Lord:

No one down here on earth seems to be able to give me an answer to a problem that has been bothering me now for some time. I wonder whether you might be able to help if I outline the various facets of the problem.

It irks me to have the Dean of Medicine tell me that we can't do anything because of a shortage of funds.

It irks me when I hear members of the staff blame the Dean for everything bad that happens—even if they are right.

It irks me to have the various departmental chairman continually holding the torch for the great urgency and necessity for research.

It irks me to hear clinical surgeons state that research is of secondary importance in a university centre.

It irks me to have the administration in the hospital continually make one-sided decisions and implement them without due recourse to those who are most affected.

It irks me to hear the professional staff say that the administration is no good—when, in fact, they do a tremendous amount to make our lives a little easier and more pleasant.

It irks me to hear that our residents don't get enough cutting to do.

It irks me to hear that university surgeons are not spending more time in teaching and instructing our residents.

It irks me to hear that our medical students are pushing to take over the running of the university and the hospital.

It irks me to hear the senior citizens in surgery saying that there is no place for students in the running of the faculty.

It irks me to see a certain degree of the "hippie" syndrome entering the clinical years of our medical course.

It irks me to hear that a medical student with a scraggly beard and dirty shoulder-length hair should be ruthlessly castigated when indeed he should just be castigated.

It irks me to see some nurses who look upon nursing as an 8-hour-a-day job.

It irks me to have our nurses blamed for every conceivable thing that happens in the hospital.

Lord, my problem is, do you think I irk too easily?

P.S. Perhaps after all it is just a sign of old age and I should think about retiring.

P.P.S. Perhaps if I took a middle course between the two extremes of each facet of my problem I might come up with the answer. Perhaps there IS a place for conservative radicalism.

ANONYMOUS

University of Toronto,
Toronto, Ont.

HYPOXEMIA IN ANESTHESIA AND SURGERY

Adequate ventilation during and after surgery has become accepted by surgeons as a desirable goal. On the other hand, its crucial and daily significance tends to be forgotten.

After general anesthesia and a major operation the patient frequently has reduced oxygen tension in arterial blood when he is breathing air. While not readily discernible as cyanosis, hypoxemia is there if you look for it by doing blood-gas analyses. Chronic hypoxemia in the first postoperative days has more than academic importance. It may produce a spectrum of disorders ranging from prolonged convalescence to myocardial infarction in patients who have unsuspected coronary disease.

Postoperative hypoxemia is caused chiefly by the pathologic exaggeration of a physiologic process in the lungs, that of shunting. Physiologic shunting is defined as that portion of right ventricular output which arrives in the left atrium without being reoxygenated. This shunting has several components. Normally, the anatomic component is about 2% of cardiac output and varies little. Another component is that due to atelectasis. A small proportion of the many millions of alveoli in normal lungs of a supine man may be collapsed at any moment, mainly in the dependent portions. Sufficient perfusion continues past recently collapsed alveoli to increase the right-to-left shunt. This results in a greater alve-

olar-arterial difference in oxygen tension (normally about 20 mm. Hg, breathing air) with, of course, a lower arterial tension. The third component of shunting comes about from uneven distribution of ventilation to perfusion throughout the lung; this effect can be eliminated by substituting oxygen for nitrogen in the alveoli.

During anesthesia, the alveolar-arterial gradient of oxygen tension, even in normal lungs, widens because of collapse of more alveoli. This diffuse atelectasis seems to be a feature of general anesthesia unrelated to the anesthetic agent used, but is greater with hypoventilation. Alveolar collapse is minimized by ventilating the patient with a deep tidal volume at a slow rate. Another implication is that the physician should give at least 30% oxygen to healthy patients and 50% or more to those who have cardiac or pulmonary disease.

After a major operation, reduced alveolar ventilation seems likely because of incisional pain and because of the use of analgesic or sedative drugs. Both pain and these drugs inhibit the tendency to sigh which is the body's normal reflex mechanism to reopen alveoli. Consequently, these patients often have arterial oxygen tensions, when breathing air, of 50 to 70 mm. Hg (accepting the relatively low figure of 70 as the lower limit of normal). Since obstruction of bronchioles leads to distal alveolar collapse as a result of absorption of trapped gas, it is essential to prevent and correct accumulation of mucus in the bronchial tree. Not many hospitals have available the capability for thorough chest physiotherapy, but simpler reasonably effective techniques are feasible in any hospital: changing body position frequently (side-back-side), forced deep breathing and coughing at regular intervals, and intermittent positive pressure breathing. Judicious sparing use of narcotics will avoid depression of the respiratory centre. Early dangling of the legs and ambulation also encourage better alveolar ventilation as well as helping the peripheral circulation.

Just as during anesthesia, most patients who remain relatively immobile in the first days after operation benefit from an inspired oxygen concentration greater than that in air, because of the exaggerated amount of shunting in their lungs. The more major the operation and the greater the immobility, the more the patient needs oxygen and a vigorous "stir-up" regimen. These methods should aid in speedier convalescence, fewer complications, and fewer tragedies such as myocardial infarction.

E. A. Moffitt

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ELEMENTAL DIET IN THE MANAGEMENT OF THE INTESTINAL LESION PRODUCED BY 5-FLUOROURACIL IN THE RAT*

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Sherbrooke, Que.

"J'admets, d'après mes expériences, qu'il y a à la surface de la membrane muqueuse intestinale une véritable génération d'éléments épithéliaux qui attirent et modifient les principes premiers résultant de la dissolution digestive, les élaborent avant de les faire passer dans les vaisseaux."

CLAUDE BERNARD,
"Leçons sur le diabète et la glycogénèse animale", p. 436, 1877.

IN our previous studies of ischemic enteropathy, we showed the value of a hydrolyzed or "elemental" diet in protecting the intestinal epithelium against irreversible necrosis produced by hypoperfusion or short-term ischemia.[1]

The present paper describes our observations on the effects of a similar elemental diet upon the changes produced by 5-fluorouracil (5-FU) in the intestinal mucosa of the rat.

When injected, 5-FU is picked up by rapidly proliferating cells and incorporated into the ribonucleic and deoxyribonucleic acid as a substitute for uracil, and suppresses DNA and RNA production.[2] The effect of DNA and RNA deprivation is greatest on the cells of certain tumours, the bone marrow and the intestinal mucosa.[3, 4] As a consequence, the dosages of 5-FU large enough to suppress tumour growth are often limited by hematologic and/or intestinal toxicity.

MATERIAL

Two hundred and fourteen young male Wistar rats,¶ weighing between 350 and 400 g., were housed in groups of two or four in wire-bottomed cages, 45 x 61 cm. in area, to prevent coprophagy. Control rats were similarly housed.

Three types of diet were used. The first, a control diet, consisted of Purina rat chow and will be referred to as Diet A or control 1. The second, a test diet, consisted of highly hydrolyzed food as described in Table I and will be referred to as Diet B

TABLE I.—COMPOSITION OF THE ELEMENTAL DIET (DIET B)

Components	*g. %*
Mead Johnson casein hydrolysate*	24.9
Sucrose	44.7
Mead Johnson medium-chain triglycerides*	6.9
Corn oil	4.3
Olive oil	10.4
Cod liver oil	1.3
Vitamin mixture†	2.5
Salt mixture (Hegsted)‡	5.0

*Mead Johnson Company of Canada Ltd., Belleville, Ont.
†Vitamin diet fortification mixture, Nutritional Biochemical Corporation, Cleveland, Ohio.
‡Nutritional Biochemical Corporation.

or elemental diet. The third diet, an additional control, differed from Diet B only in that enzymatic casein hydrolysate was replaced by an equal amount of whole casein. This diet (Diet C or control 2) will be used to investigate, in further experiments, the specific effect of feeding amino acids as compared with whole proteins. The diets were administered *ad libitum* in powder form from stainless steel cups designed to reduce spillage. All animals drank water *ad libitum*. In the elemental diet (Diet B), the concentration of fat, carbohydrate, proteins, minerals and vitamins was compatible with the recommended requirements for rats.[5] The rats given 5-FU received the drug intraperitoneally (i.p.) after eight days on the appropriate diet.

Eight series of experiments were conducted.

(1) In 48 rats we studied the effect of

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¶Ferme et Laboratoires Canadiens d'élevage Ltée, 188 rue Lasalle, Laprairie, Que.

TABLE II.—Series 1. The Effect of the Three Dietary Regimens Upon Growth, Hemograms and Height of the Jejunal Mucosa. Values Expressed as Mean ± SEM. Number of Animals in Brackets

Length of treatment (days)	Diet	BEFORE	AFTER						
		Weight (g.)	Weight (g.)	Hematocrit (%)	Hemoglobin (mg./100 ml.)	Red blood cell count (/c.mm.)	Leukocyte count (/c.mm.)	Height of mucosa (μ)	No. of villi/1.1 mm.
10	Diet A (control 1) (6)	342 ±13.4	380 ±10.61	44.9 ±1.6	14.86 ±0.33	7,850,000 ±683,000	7033 ±570	684 ± 19.00	14.3 ± 1.42
	Diet B (elemental) (7)	364 ±11.66	391 ±6.97	44.7 ±0.8	15.10 ±0.23	8,120,000 ±194,800	6757 ±550	704.33 ± 26.25	16.3 ± 0.77
	Diet C (control 2) (7)	341 ±4	368 ±9.9	42.7 ±0.83	14.13 ±0.42	7,650,000 ±132,790	6725 ±240	708 ± 20.40	16 ± 1.20
24	Diet A (control 1) (8)	371 ±24.8	409 ±23.8	44.7 ±1.1	15.25 ±0.33	8,136,000 ±227,720	6313 ±705	646 ± 34.15	13.9 ± 1.39
	Diet B (elemental) (11)	378 ±12.8	407 ±11.5	44.36 ±1.2	15.25 ±0.27	8,435,000 ±136,177	6160 ±536	701 ± 24.00	16.75 ± 0.55
	Diet C (control 2) (9)	370 ±4.2	415 ±13.2	44.4 ±0.95	15.22 ±0.42	7,540,000 ±196,333	5800 ±518	680 ± 17.83	17.6 ± 0.44

all three diets upon intestinal mucosa, hemograms and body growth in young adult rats (Table II).

In the second and third series we observed the changes in the intestinal mucosa, hemograms and body weight at different time intervals after 5-FU in relation to the diet:

(2) Eight rats received Diet A (control 1) and eight rats Diet B (elemental) for eight days, then 150 mg. of 5-FU was injected and the diet continued until sacrifice. Three rats in each group were sacrificed at five hours, and five rats at three days after 5-FU injection (Table III).

(3) Two groups of eight rats each ate respectively Diet A (control 1) and Diet B (elemental) for eight days before and until death after a single i.p. injection of 150 mg. of 5-FU. Four rats in each group were sacrificed five and six days respectively after injection (Tables IV and V).

(4) In this series we studied the 20-day survival of two groups of 25 rats each. Control animals ate Diet A, the other group Diet B for eight days before and following a single i.p. injection of 200 mg. of 5-FU. The surviving rats were sacrificed

TABLE III.—Series 2. Changes of Intestinal Mucosa, Body Weight and Hemograms, Three Days After i.p. Injection of 150 mg. of 5-FU. Values Expressed as Mean ± SEM. Number of Animals in Brackets

	Height of mucosa (μ)			Hematocrit (%)	Hemoglobin (mg./100 ml.)	Red blood cell count (/c.mm.)	Leukocyte count (/c.mm.)	Weight lost (%)
	Jejunum	Ileum	Colon					
Diet A (control 1) (5)	335 ±18	357 ±30	363 ±18	54 ±2.7	18.9 ±0.68	9,403,600 ±279,556	1220 ±174	10.6
Diet B (elemental) (5)	373 ±15	400 ±17	411 ±25	57 ±2	19.86 ±0.57	9,432,000 ±230,000	1520 ±363	11.7

Diet A (control 1) (5)

Jejunum: Total loss of villus structure in two rats; the epithelium was either absent or represented by vacuolated foamy remnants of cuboidal or flat cells. Most villi were fused except on the tip.
Ileum: Similar picture although the villus structure was better preserved.
Colon: Reduced superficial mucin, small areas of epithelial necrosis on the surface.
In all cases the crypts appeared distorted and dilated with exudate often with lymphocytes; similarly, the lamina propria was infiltrated.

Diet B (elemental) (5)

Jejunum: In four rats, the epithelium was still columnar, although vacuolated in many areas (in one of these the epithelium appeared normal); one rat showed flat cells on the side of the villus with cuboidal cells on the tips. The villus structure was maintained in most cases; only in two rats was a slight fusion of villi observed in a few areas.
Ileum: Similar to jejunum.
Colon: Reduced mucin; in one rat there were a few small areas of epithelial damage.
In both controls and diet rats, congestion and interstitial hemorrhages were seen in the submucosa.

20 days after 5-FU (Table VI).

(5) Three groups of eight rats ate Diets A, B and C (control 2) respectively for eight days before and after a single i.p. injection of 150 mg. of 5-FU. They were sacrificed three days after injection (Table VII).

Three final experiments were carried out to elucidate the mechanisms of the protection afforded by Diet B (elemental). In these, we studied the tryptic activity in the chyme as well as peptidase, sucrase

TABLE IV.—Series 3. Changes of Intestinal Mucosa, Body Weight and Hemograms Five and Six Days After i.p. Injection of 150 mg. of 5-FU. Values Expressed as Mean ± SEM. Number of Animals in Brackets

	Hematocrit (%)	*Hemoglobin* (*mg./100 ml.*)	*Red blood cell count* (*/c.mm.*)	*Leukocyte count* (*/c.mm.*)	*Neutrophils* (%)	*Lymphocytes* (%)	*Monocytes* (%)	*Weight lost* (%)
Diet A (control 1) (8)	41.3 ±0.9	15 ±0.3	7,970,000 ±230,000	2233 ±500	4.5 ±1.1	95 ±1.1	0.5 ±0.2	12.4
Diet B (elemental) (8)	41.2 ±1	15 ±0.4	8,010,000 ±172,000	2161 ±290	8.4 ±2.5	90 ±2.7	1 ±0.4	11.3

	Height of mucosa (μ)		*No. of villi/1.1 mm.*	
	5 days	*6 days*	*5 days*	*6 days*
Diet A (control 1) (4)	441 ±34	628 ±22	12 ±0.4	10.2 ±1.5
Diet B (elemental) (4)	495 ±56	613 ±29	12.6 ±0.5	11.3 ±0.4

TABLE V.—Series 3. Number of Large Phagocytic Vacuoles and Villi per Section in the Absorbing Cells of the Intestine Five Days After i.p. Injection of 150 mg. of 5-FU (Transverse Sections of Approximately 0.8 cm.). Number of Rats in Brackets

	Diet A (*control 1*) (*4*)		*Diet B* (*elemental*) (*4*)	
	No. of large vacuoles	*No. of villi*	*No. of large vacuoles*	*No. of villi*
Jejunum	1	67	0	100
Ileum	7	114	0	98
Jejunum	0	90	0	86
Ileum	44	30	0	79
Jejunum	7	85	0	100
Ileum	8	120	0	114
Jejunum	82	106	0	61
Ileum	57	86	0	113
Mean	26	87	0	93

TABLE VI.—Series 4. Single i.p. Injection of 200 mg. of 5-FU in 50 Rats. Effects on Survival, Body Weight, Pathology and Hemograms. Values Expressed as Mean ± SEM. Number of Animals in Brackets

		No. of days before and after 5-FU				
		—10	*Injection*	*+5*	*+8*	*+20*
Body weight (*g.*)	Diet A (control 1) (25)	a 422 ±3.9 (25)	b 444 ±4.2 (25)	c 375 ±4.6 (22)	d 371 ±6.3 (20)	e 380 ±9.8 (9)
	Diet B (elemental) (25)	a^1 413 ±6 (25)	b^1 449 ±5.5 (25)	c^1 392 ±6 (25)	d^1 376 ±7 (25)	e^1 448 ±15 (8)

c vs c^1: $P < 0.05$ e vs e^1: $P < 0.01$

		Hematocrit (%)	*Hemoglobin* (*mg./100 ml.*)	*Red blood cell count* (*/c.mm.*)	*Leukocyte count* (*/c.mm.*)	*Neutrophils* (%)	*Lymphocytes* (%)	*Monocytes* (%)	*Eosinophils* (%)	*Basophils* (%)
Hemograms in survivors sacrificed 20 days after injection of 5-FU	Diet A (control 1) (9)	35.96 ±1.8	11.95 ±0.64	5,542,500 ±466,046	a 5362 ±1335	38 ±2.8	62 ±2.8	0.5 ±0.26	0.12 ±0.1	0
	Diet B (elemental) (8)	36.90 ±1.86	12.68 ±0.30	6,521,666 ±265,457	b 10,720 ±1238	28 ±5.5	70 ±5	1.16 ±0.4	0.16 ±0.1	0.5 ±0.2

a vs b: $P < 0.05$

Postmortem Pathology

First phase (intestinal): first week.—In the control group, five rats died from three to seven days after 5-FU with massive necrosis of the intestinal mucosa. None died in the diet group.

Second phase (general toxicity): second and third weeks.—The majority of rats died from 10 to 16 days after 5-FU, 11 in the control and 17 in the diet group. The intestine appeared normal in all animals (possibly regeneration of mucosa). The liver and pancreas showed numerous areas of cellular necrosis with edema; in the kidneys there was severe tubular necrosis and some glomerulitis.

TABLE VII.—Series 5. Changes of Intestinal Mucosa, Hemograms and Weight Loss in Three Groups of Rats Under Different Dietary Regimens, Three Days After a Single i.p. Injection of 150 mg. of 5-FU. Values Expressed as Mean ± SEM. Number of Animals in Brackets

	Height of mucosa (μ)		*Hematocrit* (%)	*Hemoglobin* (*mg./100 ml.*)	*Red blood cell count* (*/c.mm.*)	*Leukocyte count* (*/c.mm.*)	*Neutrophils* (%)	*Lymphocytes* (%)	*Weight lost* (%)
	Jejunum	*Ileum*							
Diet A (control 1) (8)	a 353 ±13	b 489 ±26	43.8 ±0.6	16.5 ±0.2	8,368,570 ±137,244	3080 ±568	22.5 ±3.1	77.2 ±3.1	12.2
Diet C (control 2) (8)	390 ±11	c 478 ±19	44.2 ±0.7	16 ±0.2	8,371,250 ±174,146	3400 ±610	18 ±1.7	82 ±1.7	11
Diet B (elemental) (8)	a^1 428 ±12	b^1 576 ±13	44.7 ±1	17 ±0.3	8,550,000 ±294,144	3242 ±416	20 ±3.7	80 ±3.0	10
	a vs a^1: P <0.005		b vs b^1: P <0.025		c vs b^1: P <0.005				

Histology of the Ileum

Diet A (control 1) (8)	In four rats the villus structure was lost in many areas, the epithelial cells were cuboidal, shrunken or necrotic. In four other rats some villi were fused, with a very pale columnar epithelium near the tip. Most crypts had lost their normal cellular lining and there were only isolated nests of a few epithelial cells.
Diet C (control 2) (8)	In two rats the villus structure was lost; in one, necrotic cuboidal epithelium covered the tip of fused villi; in four rats some villi were fused and the columnar epithelium was very pale near the tips; one rat was normal. Most crypts had lost their normal cellular lining and there were only isolated nests of a few epithelial cells.
Diet B (elemental) (8)	In five rats the villi were normal, only the columnar cells on the tip of some villi appeared pale. In three rats, the villi and epithelium were normal. In all animals the crypts maintained normal structure.

In all groups the same degree of submucosal hemorrhage was seen.

and alkaline phosphatase activity in the homogenate of the ileal mucosa:

(6) In this experiment, used as a control for series 7 and 8, two groups of 10 rats each were sacrificed after eight days on Diets B and C respectively.

(7) Two groups of 10 rats ate respectively Diets B and C for eight days before and after i.p. injection of 150 mg. of 5-FU; the animals were sacrificed 24 hours after injection.

(8) These 20 rats (10 rats on Diet B and 10 on Diet C) were treated like those in series 7, but the time of sacrifice was three days after 5-FU injection. In this last series, the average daily intake of food and calories was determined before and after 5-FU (Table VIII).

Methods

Five-fluorouracil injection and sacrifice were both done under ether anesthesia. These procedures were done at approximately the same time of day in rats fasted overnight.

The samples of intestine used for histology were taken *in vivo* from the jejunum (immediately distal to the ligament of Treitz), from the terminal ileum (8 cm. from the cecum) and from the terminal colon. The specimens were fixed in Bouin solution, in 1% buffered osmium tetroxide, or in 3% buffered glutaraldehyde depending on the purpose of the study. After dehydration they were imbedded in paraffin or in Epon.

For mitotic count, the number of cells in mitosis (metaphase) in approximately 30 crypts was counted for a total of 2000 nuclei.

Mucosal height was measured with a micrometer scale from the base of the crypt to the apex of the villus. The values reported represent the average for 20 villi.

For the cytochemical studies, material fixed in 3% glutaraldehyde was sectioned

TABLE VIII.—Series 8. Daily Food Intake and Body Growth With Two Dietary Regimens. Effect of 150 mg. of 5-FU Given on the Ninth Day of Diet Upon Food Intake and Body Weight (Three Days Follow-Up). Values Expressed as Mean ± SEM. Number of Rats in Brackets

	Daily food intake				*Weight*		
	g./day		*cal./day*				
	Control period	*Daily mean after 5-FU*	*Control period*	*Daily mean after 5-FU*	*Initial weight (g.) control period 1st day*	*Growth rate (g./day) control period*	*Weight loss 3 days after 5-FU* (%)
Diet B (elemental) (10)	24.1 ±1	3.2 ±0.3	115.7 ±4.8	15 ±1.4	319 ±6	4.1 ±0.4	11
Diet C (control 2) (10)	23.2 ±0.8	3.7 ±0.5	111.4 ±3.8	17.7 ±2.4	324 ±8	4.9 ±0.3	12

at 8 μ with a freezing microtome. For optical determination of alkaline phosphatase activity, reactions were made in the medium of Burstone.[6] For ultrastructural examination, the grids, covered with the fine sections, were examined under an E.M. 300 Philips electron microscope.

Chyme for analysis of tryptic activity was collected in the following manner: 4 c.c. of ice-cold saline was introduced in the duodenum with the pylorus and terminal ileum clamped. After mixing, the content was analyzed for tryptic activity with the Boehringer colourimetric method using 0.01 M arginine-p-nitranilide as substrate. The results were expressed in mU (unit is abbreviated to U and milliunit to mU); a unit is defined as the amount of enzyme that converts 1 micromole of substrate per minute under highly optimal conditions at 25° C. Samples of blood were taken by exsanguination to determine the red blood count, white blood count and hematocrit.

Serum alkaline phosphatase of intestinal origin was determined by electrophoresis on polyacrylamide disc gels.[7] For biochemical analysis of the mucosal homogenate, the intestine was removed immediately after sacrifice and was flushed from the pylorus to the cecum with ice-cold saline until clean. The whole mucosa was gently scraped from the entire length of the excised gut at 4° C. with a glass blade; the specimens were then stored at −20° C. Our previous experiments confirmed that dipeptidase[8] and sucrase[9] activities are stable for at least three months at this temperature. These activities were determined in the supernatant of the homogenate after centrifugation at 27,000 G. Dipeptidase activity (glycine L-leucine and glycine L-valine) was measured according to the method of Josefsson and Lindberg.[10] The accuracy of this method is about ± 1% and it is much more sensitive than the procedures commonly used hitherto.[11] One unit of dipeptidase activity is defined as the activity hydrolyzing 1 micromole of dipeptide per minute at 40° C. The activity is expressed as units per milligram of nitrogen. Sucrase activity in the supernatant of the mucosal homogenate was determined by the method of Dahlqvist.[12] The disaccharidase unit is defined as the activity hydrolyzing 1 micromole of disaccharide per minute and is expressed as millimicromoles of glucose per minute per milligram of protein. Alkaline phosphatase in the supernatant was measured at pH 10, using paranitrophenylphosphate (PNPP) as substrate, and is expressed in millimicromoles of paranitrophenol (PNP)/min./mg. protein. Protein was measured using the method of Lowry *et al.*[13] The nitrogen content was calculated as 17% of the protein content. Tissues and serum of all rats in each group were pooled before analysis; the result expressed the average obtained in each group. Since no deaths were recorded after 5-FU in the period of study, all groups contained the same number of rats—10 each.

Results

Our studies show that it is feasible to maintain rats for at least 24 days on a diet in which amino acids represent the protein fraction, a disaccharide represents the carbohydrates, while 30% of the lipids are in the form of medium-chain triglycerides. This diet maintained body growth at a rate comparable to controls, and the hemograms were normal at the end of the observation period (Table II). The visceral organs had a normal appearance. Despite the reduced demand upon digestive function, examination of the pancreas revealed no sign of atrophy; the gland was normal grossly and microscopically and tryptic activity was normal in the chyme in the fasting phase (Table IX, Series 6 and 8). Furthermore, in all groups injected with 5-FU, the average growth in the eight days before injection was similar irrespective of the diet.

The mucosa of the small bowel after Diet B (elemental) can be described as follows: the cells in the epithelium were of normal size with a slightly thicker mucus coat, and there was no difference in subcellular structure. The lamina propria was unchanged in size and cellular pattern. Similarly, the average height of the mucosa was essentially unchanged (Table II). The percentage of mitoses in the crypts of the

TABLE IX.—SERIES 6 (CONTROL) AND 8. TRYPTIC ACTIVITY IN THE CHYME AFTER OVERNIGHT FASTING, FOLLOWING EIGHT DAYS ON THREE DIFFERENT DIETARY REGIMENS; IN SERIES 8 THE CHYME WAS OBTAINED IN A SIMILAR MANNER AFTER 12 DAYS OF DIET, BUT ON THE NINTH DAY 150 MG. OF 5-FU WAS INJECTED I.P. VALUES EXPRESSED AS MEAN ± SEM. NUMBER OF ANIMALS IN BRACKETS

	Tryptic activity of the chyme (mU/mg. dry weight)	
	Series 6 no 5-FU	*Series 8 5-FU*
Diet A (control 1) (10)	20 ± 2	21 ± 1.8
Diet B (elemental) (10)	22.8 ± 1.8	18.8 ± 2
Diet C (control 2) (10)	24 ± 2.6	19.6 ± 2.5

jejunum was found to average 3.69 ± 0.2 in controls (Diet A) and 3.9 ± 0.14 in rats on Diet B.[14]

A single injection of a high dose of 5-FU was followed by changes in the small-bowel mucosa which varied in relation to the dietary regimen.

In the controls three days after 5-FU (Table III, series 2) the intestine showed total atony throughout its entire length, edema and congestion; the chyme was often bloody with abundant fluid in the lumen. Conversely, in the rats on Diet B the tonicity was nearly normal in most cases, with no edema; only the colon was hypotonic. The intestinal content was green and was made up chiefly of biliary secretions. The height of the jejunal and ileal mucosa and the detailed description in Table III confirm the microscopic differences between the two groups: in the Diet-B group the villus structure is nearly always preserved and the epithelium, though often pale and shrunken, is usually preserved as opposed to the extensive necrosis seen in controls (Figs. 1-4). Similar differences are seen in the terminal colon (Figs. 5 and 6).

In series 3, observed on the fifth and sixth days after 5-FU injection, the mucosa had regenerated and a casual look on light microscopy showed a villus pattern essentially normal in both groups except for a few areas of partial coalescence as evidence of previous damage. However, in control rats at the fifth day, the absorbing cells near the apex contained a significant number of large phagocytic vacuoles. These elements were totally absent in rats on the elemental diet (Diet B) and both elemental and control rats on the sixth day (Table V). It is reasonable to speculate that vacuoles in such large numbers represent remnants of focal cytoplasmic necrosis which occurred in the crypts in the early days after 5-FU injection. The cellular inclusions migrate with the cell towards the apex of the villus and are shed in the lumen with the cell by the sixth day. In retrospect, this provides another indication of the more extensive cellular autolysis in control rats.

In series 4 (Table VI) we have assumed that irreversible extraintestinal damage caused by the high (200 mg.) dose of 5-FU masked the effect of the "intestinal factor"* on the 20-day survival. Nevertheless, there were no "intestinal deaths" within the first week in the diet group while 20% of controls suffered such deaths. Although at the third day, the blood counts were similar in both groups, at 20 days after 5-FU there were more red and white cells in the blood of the diet survivors. The extraintestinal effects of Diet B were also expressed in the body weight after 5-FU in all series: for the first three to five days after 5-FU the average percentage weight loss was always less in the diet group than in their respective controls (Tables III, IV and VII). Although the differences within each series may be below statistical significance, the constant trend in all series suggests that, when the mucosa is better preserved, the rats have a better capacity for absorption and nutrition and have less intraluminal fluid loss.

In order to define better the role of the diet, we studied a fifth series in which whole casein was substituted for casein hydrolysate in the formula described in Table I—this is Diet C. The only variable in this series was the hydrolysis of the protein fraction. Objective measurement of the height of the mucosa and evaluation of the histologic appearance after 5-FU

*The "intestinal factor" in the literature on shock refers to the systemic effect of the intestinal lesion.

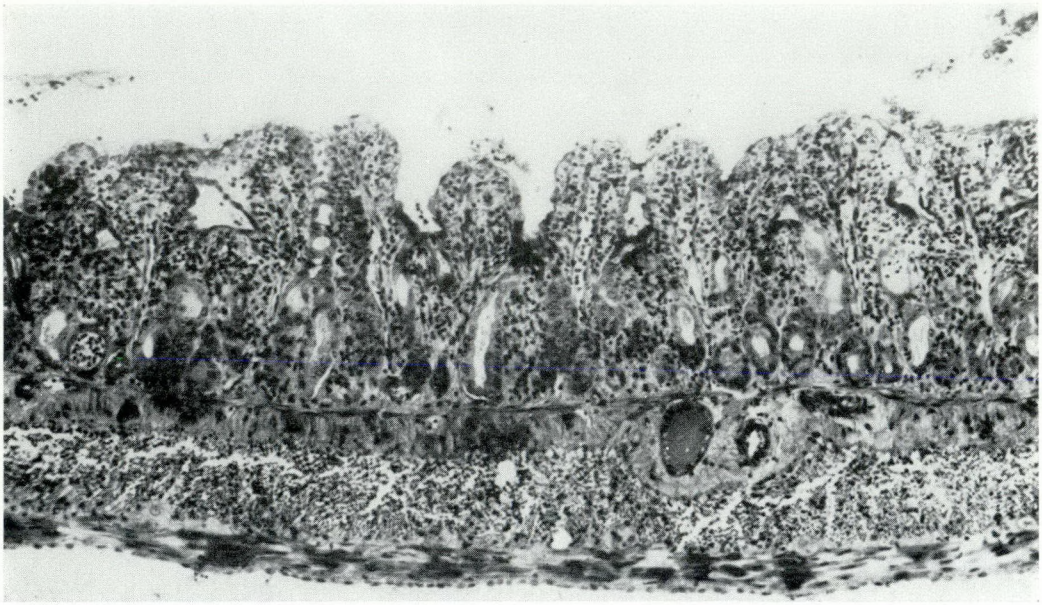

Fig. 1.—Jejunum of a rat three days after the injection of 150 mg. of 5-FU. A representative example of the worst lesion seen in the group on Diet A (control 1); there is total loss of villus structure, and dilated crypts (× 95).

Fig. 2.—Jejunum of a rat three days after the injection of 150 mg. of 5-FU. A representative example of the worst lesion seen in the group on Diet B (elemental). Despite severe degeneration of the lining epithelium, the villus structure is essentially maintained. At the bottom of the mucosa there are numerous nests of crypt cells (× 95).

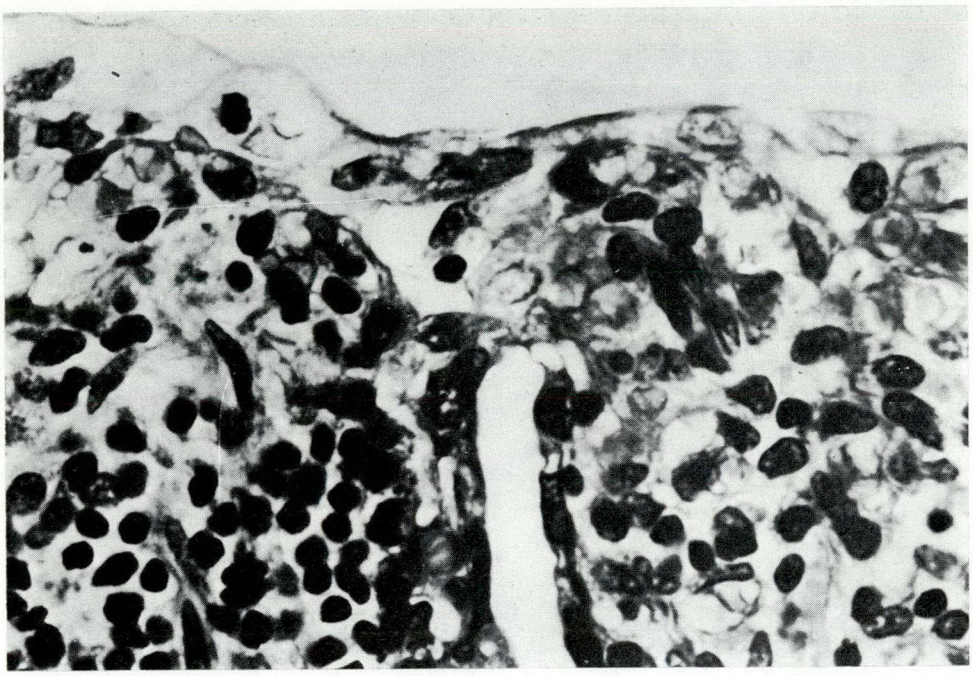

Fig. 3.—Jejunum of a rat three days after the injection of 150 mg. of 5-FU. A representative example of the mildest form of lesion seen in the group on Diet A (control 1). The large dilated flattened villus is covered with small cuboidal epithelial cells (original magnification × 600).

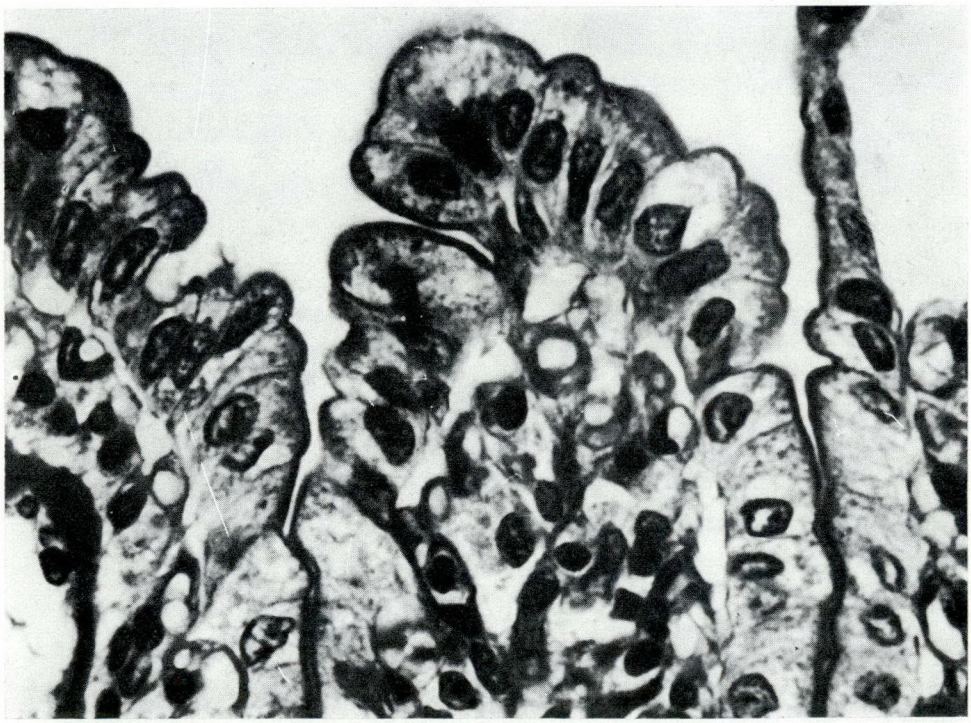

Fig. 4.—Jejunum of a rat three days after the injection of 150 mg. of 5-FU. A representative example of the best preserved mucosa seen in the group on Diet B (elemental). The mucosa is relatively normal with few distorted absorbing cells (original magnification × 600).

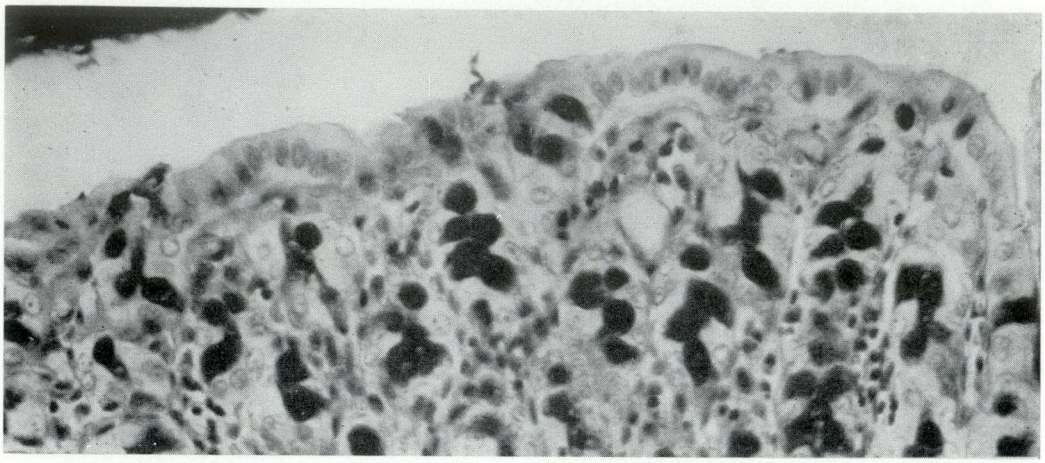

Fig. 5.—Terminal colon of a rat three days after the injection of 150 mg. of 5-FU. A representative example seen in the group eating Diet B (elemental) (× 350).

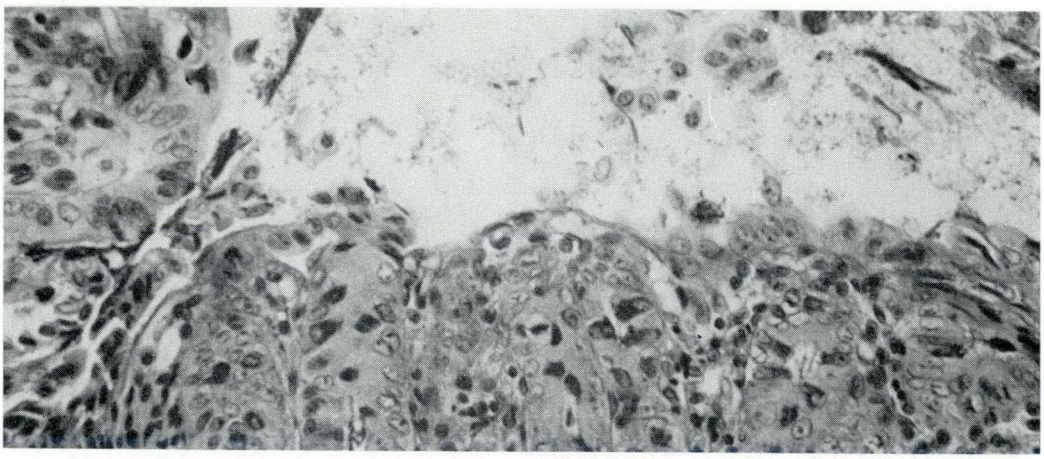

Fig. 6.—Terminal colon of a rat three days after 150 mg. of 5-FU. A representative example seen in the group eating Diet C (control 2) (× 350).

provided clear evidence of the superiority of casein hydrolysate over whole casein (Table VII). In effect, the rats receiving whole casein in the diet (Diet C) fared only slightly better than rats on Purina rat chow (Diet A). In our subsequent experi-

TABLE X.—Series 6, 7 and 8. Effect of Elemental Diet and 5-FU (Singly or Combined) on Intestinal Mucosal Enzymes. Values Expressed as Mean ± SEM. Number of Rats in Brackets*

	Series 6 *No 5-FU*		*Series 7* *24 hours after 5-FU*		*Series 8* *3 days after 5-FU*	
	Diet C (control 2) (10)	Diet B (elemental) (10)	Diet C (control 2) (10)	Diet B (elemental) (10)	Diet C (control 2) (10)	Diet B (elemental) (10)
Alkaline phosphatase	0.812 ±0.072	0.531 ±0.051	11.42 ±1.4	14.5 ±1.92	2.39 ±0.41	2.00 ±0.36
Sucrase	6.86 ±0.72	6.51 ±0.62	19.25 ±2.02	22.8 ±2.17	1.97 ±0.15	1.508 ±0.06
Dipeptidases						
Glycine-L-valine	25.8	1.58	0.6	0.6	0.4	0.5
Glycine-L-leucine	38.82	4.1	5.03	4.7	1.0	1.2

*Enzymatic activities in homogenate of ileal mucosal scrapings for each group of 10 rats on different dietary regimens, before and after 150 mg. of 5-FU. Each value represents the enzymatic activity of the pooled tissues of each group of 10 animals. The standard deviations (±) for alkaline phosphatase and sucrase represent the variations of repeated (8) analysis of the same pooled sample. Standard deviations are not expressed for dipeptidases as we have confirmed, in repeated analysis, the accuracy of the method (±1%) reported by Josefsson. A dramatic fall in dipeptidase is observed with the use of the elemental diet alone (adaptation), or with the use of 5-FU alone (inhibition of biosynthesis). As expected, the combination of 5-FU and elemental diet results in a similar fall. Alkaline phosphatase is expressed as millimicromoles of PNP/min./mg. of proteins. Sucrase as millimicromoles of glucose/min./mg. of proteins. Dipeptidase as U/mg. of nitrogen.

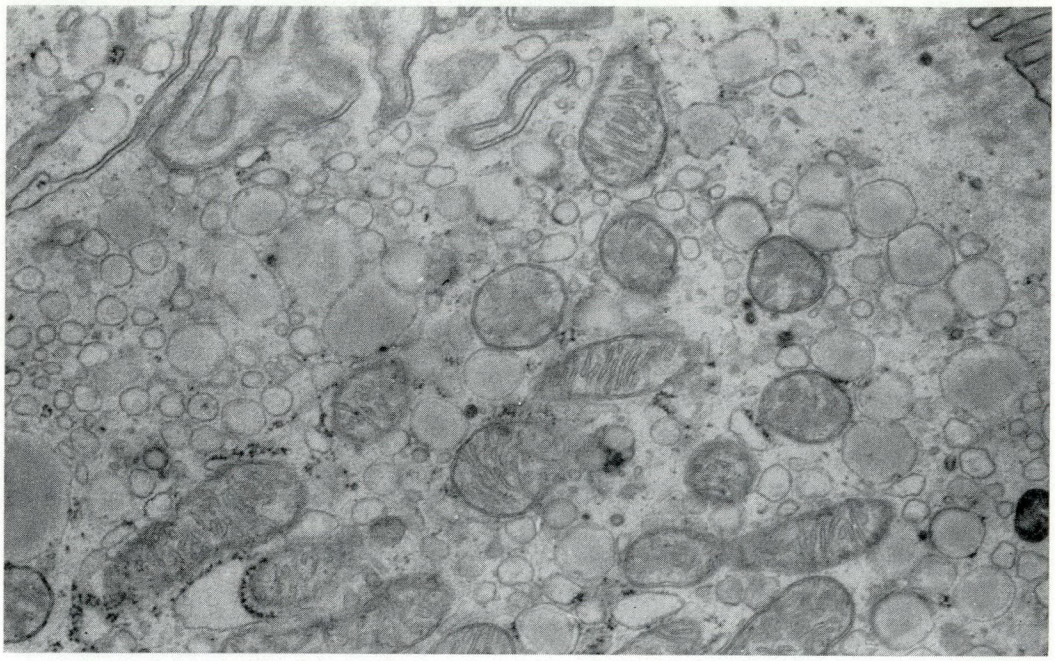

Fig. 7.—Jejunal absorptive cell of a rat on Diet C (control 2) 24 hours after the injection of 150 mg. of 5-FU. The microvilli are at the upper right of the micrograph. The cytoplasm is crowded by fat globules distending the endoplasmic reticulum. Very few chylomicrons are seen in the intercellular spaces. The number of free ribosomes is decreased (× 23,500).

ments designed to investigate the mechanism of action of the amino acid (Diet B) we have used only Diet C as control. Table X describes the effect of Diets B and C and 5-FU upon intestinal enzymes as the biochemical events are followed at time intervals after 5-FU. We have observed that the simple ingestion of amino acids (Diet B) instead of proteins (Diet C) induces an adaptation phenomenon in the absorbing cells by decreasing markedly both dipeptidases studied (Table X). Dipeptidase activity observed in our controls (Diet C) is closely similar to that reported by Josefsson and Lindberg[11] in the rat.

If we now examine the response to 5-FU of the animals on the control diet we note a pronounced activation of alkaline phosphatase and sucrase, and a sharp decrease in dipeptidases as early as 24 hours after injection (Table X) in spite of the anatomical integrity of the cells at this time (Figs. 7 and 8).

The enzymatic pattern after 5-FU injection in the animals fed the elemental diet is similar to that of the control-diet rat with the notable difference that dipeptidases have already been considerably reduced by the diet before the administration of the drug. Three days after 5-FU, the sucrase and dipeptidase activities are all below normal values whatever the diet. In the serum, the slow-moving intestinal band of alkaline phosphatase on electrophoresis has disappeared in both groups (Fig. 9), probably indicating that the source of production has been exhausted three days after 5-FU injection.

Discussion

The role of pancreatic proteases in the pathogenesis of enteric lesions associated with shock,[15, 16] uremia,[17] nitrogen mustard[18] and radiation[19] led us to define this intestinal complication as "tryptic enteritis".[16] On the practical side, however, it became apparent that while pancreatic-duct ligation or local instillation of trypsin inhibitor was effective in the animal, oral administration was ineffective in maintaining a low level of tryptic activity in the chyme. Both natural and synthetic trypsin inhibitors, when given orally, stimulate the

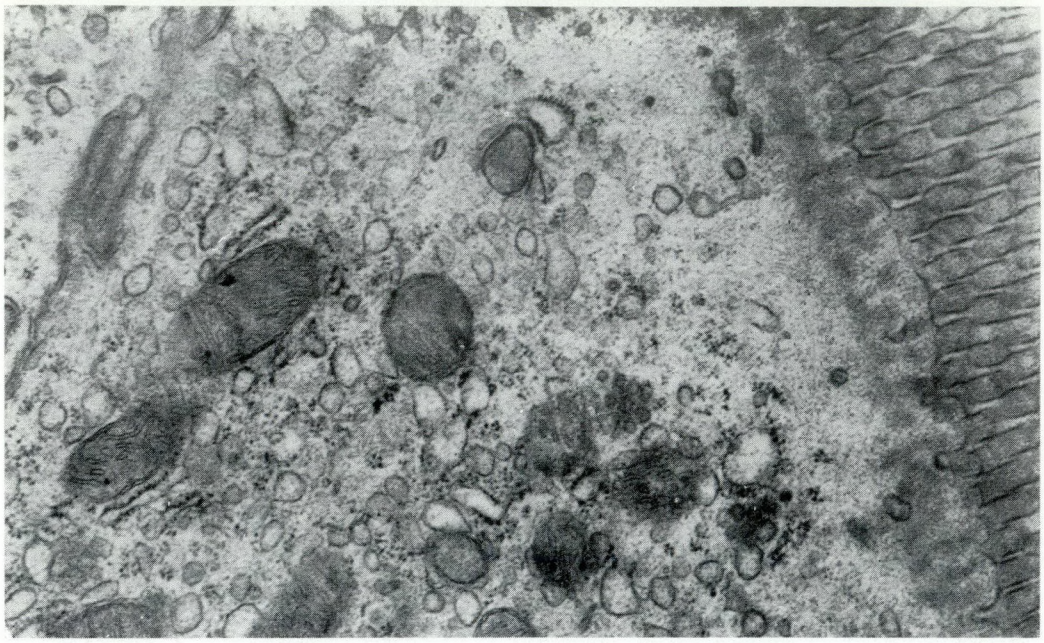

Fig. 8.—Jejunal absorptive cell of a rat on Diet B (elemental) 24 hours after the injection of 150 mg. of 5-FU. No fat globules are seen in the cytoplasm. However, numerous cisternae of rough and smooth endoplasmic reticulum are dilated into small empty vessels. Free ribosomes are abundant (× 30,200).

production of pancreatic proteases in such a way that a steady state is quickly obtained with a return to a normal or even increased tryptic activity in the chyme.[20, 21] Much experimental and clinical evidence suggests that the pancreas can adapt to variations in the kind of food ingested by secreting the appropriate enzyme or enzymes. We attempted to induce pancreatic adaptation and reduce the tryptic activity

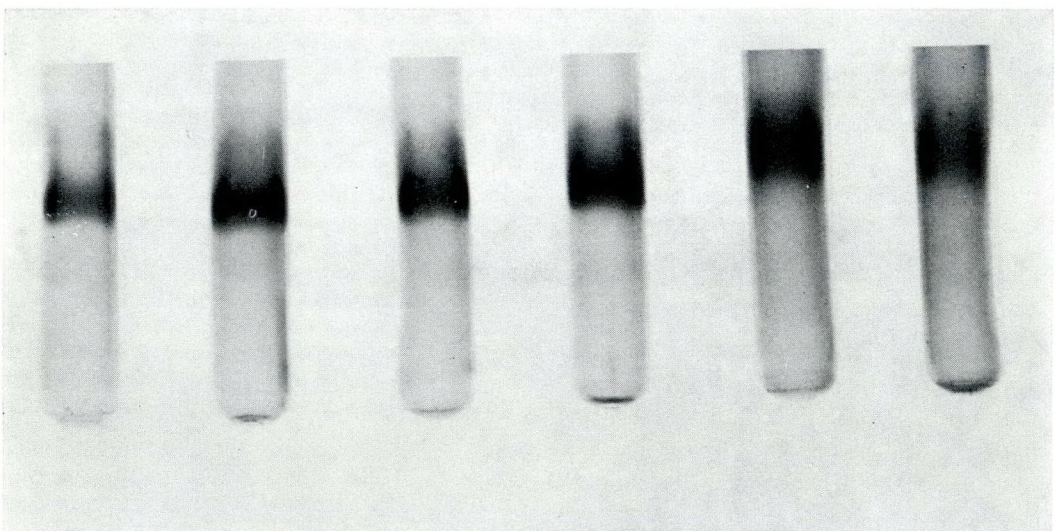

Fig. 9.—Disc electrophoresis of serum alkaline phosphatase in a continuous tris-borate buffer at pH 9.5. There were 10 rats in each group. From left to right: Diet C, control; Diet C 24 hours after 5-FU; Diet B, control; Diet B 24 hours after 5-FU; Diet C three days after 5-FU; Diet B three days after 5-FU. Note the slight accentuation of the slow-moving (lower) band (intestinal fraction) 24 hours after 5-FU and its disappearance three days after 5-FU.

in the chyme by feeding amino acids instead of protein over a period of time. Earlier this procedure was found to decrease the trypsinogen content of pancreatic tissue.[22, 23] Although the amino-acid diet failed to reduce significantly the baseline activity in the chyme of the fasting dog[1] and rat (Table IX), it protected the intestinal mucosa against shock-induced necrosis.[1]

In the present experiments, the use of an elemental diet appeared to provide significant protection of the intestinal mucosa against 5-FU toxicity. The fifth and subsequent series of experiments clearly indicated that this protection is related to the replacement of the proteins by their own enzymatic hydrolysate. In evaluating the mechanism of this protection, two factors must be considered: first, to be effective the dietary regimen has to be maintained for a certain number of days before injury; second, it must be continued throughout the observation period following injury. It has already been shown that the changes produced in the normal intestine by the elemental diet are primarily a quantitative reduction of flora[1] and bulk, and a certain increase in the thickness of the mucus coat.[14] In the absorbing cells of the intestine an enzymatic adaptation is shown to occur with marked decrease in peptidase activity (Table X). Although the baseline activity of trypsin in the chyme does not appear to be affected, the decreased enzyme storage in the pancreas reported by others[22, 23] may indeed dampen the output of proteases under stimulus. It is conceivable that all these factors play a role in facilitating the survival of the intestinal mucosa following injury. Since the percentage of cells in mitosis in the crypts is not affected by the diet,[14] the protection does not appear to reside at the level of the dividing cell. Furthermore, we have unpublished data that show that the degree of mitotic arrest five and 24 hours after 5-FU is similar in all groups.

The second aspect of the protective mechanism must operate after injury.

We shall consider here the nutritional aspect in the phase following injury and attempt to interpret our own data in the light of recent knowledge on terminal digestion. The brush-border localization of disaccharidases was demonstrated by Dahlqvist and Borgstrom[24] and Miller and Crane.[25] The locus of hydrolysis appears to be in the outer region of the microvillus membrane either in the membrane *per se*[26] or in the enteric surface coat.[27] Subsequent studies on the subcellular localization of peptidases indicated that these enzymes, too, are localized in the intestinal epithelium.[10, 11]

Pancreatic digestion releases mainly small polypeptides and a few amino acids.[28] It appears that the peptides released by peptic and pancreatic digestion are hydrolyzed by the brush-border aminopeptidase to free amino acids and dipeptides.[29] It is probable that the amino acids and dipeptides are transported into the enterocyte where the final stage of dipeptide hydrolysis occurs.[30] The predominant physiologic role for epithelial-cell peptidases in human protein digestion was suggested by studies in which ^{5}N-labelled protein was used to show that men with severe pancreatic insufficiency could absorb up to 80% of dietary protein. Conversely, in patients with normal pancreatic function but with diminished epithelial-cell peptide hydrolase activity due to celiac disease, the overall digestion and absorption of protein was delayed to a greater degree than the absorption of free amino acids.[31] At 24 hours after 5-FU, a comparable situation appeared to develop in our rats: despite a significant increase in the sucrase and alkaline phosphatase, the dipeptidase activity dropped to extremely low values. This remarkable drop of dipeptidase activity 24 hours after 5-FU, in contrast with other brush-border enzymes, may reflect a faster turnover of these proteases within the mature differentiated cells.[32] To the extent that measurement of enzymatic action in the mucosal homogenate reflects actual hydrolysis *in vivo*, one could assume that the terminal digestion of proteins is severely hampered if it does not cease entirely after 5-FU. The animals receiving amino acids would then be favoured if the transport or diffusion of amino acids is even moderately preserved. In this connection recent experiments by Hirschfield and

Kern[33] demonstrated that the intestinal cells use amino acids absorbed from the lumen to a greater degree than those supplied by a systemic route. This difference is accentuated in protein-deprived animals. The increased availability of amino acids in the elemental-diet group could help intestinal repair after injury. The constant accumulation of large fat particles in the absorbing cells of the control rats 24 hours after 5-FU injection (Fig. 7) in contrast with normal rats or rats on the elemental diet under similar circumstances (Fig. 8) may be due to their decreased ability to mobilize fat via the lipoprotein pathway, because of a reduction in available amino acids. What is good for the physiologic and anatomical integrity of the absorbing cell is good for the nutrition of the whole organism; this is reflected by the curve in body weight after injury. The beneficial effects of the amino-acid diet thus appear to be partly related to the severe impediment of terminal protein hydrolysis produced by 5-FU. The amount of food and calories ingested in the days after 5-FU does not vary significantly in the controls as compared to the rats on the amino-acid diet, but the utilization of the ingested nitrogen is conceivably superior in the diet group (Table VIII).

Summary

An elemental diet containing amino acids instead of proteins has been shown to protect the intestinal epithelium of rats against the lesions associated with the administration of 5-fluorouracil. Several factors are involved in this protection. Some of them act by altering the intestinal environment in the phase before injury; others appear to have their effects in the phase after injury. One of the striking effects of 5-FU appears to be an early drop of dipeptidase activity in the ileal mucosa. This phenomenon precedes any decrease in other enzymatic activity or changes in the ultrastructure of the absorbing cells. We postulate that a severe impediment thus develops in the terminal cellular digestion of proteins. The amino-acid diet would then make these important elements available for the nutritional and biosynthetic processes of the mucosal epithelium.

It was also observed that the intestinal epithelium adapts to an amino-acid diet by reducing sharply its dipeptidase activity.

The authors wish to thank Dr. D. Maestracci, for the analysis of enzymatic activities in the intestinal mucosa; Dr. J. E. Knapp and the Mead Johnson Company of Canada Ltd. for their scientific and technical assistance, and Dr. Bernard Perey, Chairman, Department of Surgery, University of Sherbrooke, for reviewing the manuscript.

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Résumé

Une diète élémentaire contenant des acides aminés au lieu de protéines protège l'épithélium intestinal des rats contre les lésions induites par le 5-fluorouracil (5-FU). Plusieurs facteurs entrent en jeu dans ce mécanisme protecteur. Certains d'entre eux préparent le milieu intestinal dans la phase précédant l'aggression; d'autres facteurs agissent durant le traitement: parmi les effets principaux du 5-FU, on a observé une chûte marquée de l'activité dipeptidase de la muqueuse iléale. Ce phénomène précède la baisse d'activité, d'autres enzymes et des changements ultrastructuraux des cellules absorbantes. On admet d'après ces expériences, une diminution de la digestion terminale des protéines après le 5-FU conduisant à une véritable malabsorption. Une diète à base d'acides aminés offre une meilleure disponibilité de ces éléments essentiels au phénomène de nutrition et de synthèse au niveau de l'épithélium intestinal.

On a aussi observé que l'épithélium intestinal s'adapte à une diète à base d'acides aminés en réduisant fortement son activité en dipeptidases.

ELEMENTAL DIET IN THE MANAGEMENT OF THE INTESTINAL LESION PRODUCED BY 5-FLUOROURACIL IN MAN*

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THE management of cancer with antimetabolites or radiation is often limited by the resulting hematologic or gastrointestinal toxicity. In the most severe cases the intestinal complication is characterized by nausea, diarrhea and melena. Less well-known is malabsorption without manifest clinical symptoms, which worsens the patient's nutritional state, thereby contributing to cachexia. The present study is primarily concerned with this type of enteropathy. We report the effects of an elemental diet in cancer patients receiving 5-FU with or without radiation. Previous studies described elsewhere in this issue (p. 298) provided evidence that a similar diet protects rats against experimental 5-FU enteropathy.[1]

MATERIAL AND METHODS

Twenty-four patients, 17 men and seven women, with proved advanced metastatic carcinoma were selected for study. All patients received a standard dose of 5-FU (12 mg./kg. body weight) which was given intravenously in 250 ml. of 0.9% NaCl in water over a two-hour period. The usual course was a full dose for six to nine consecutive days; in a few cases, the last two doses were given two days apart. The patients were assigned alternately to two groups, one eating normal hospital food *ad libitum* (control group), the other one eating the elemental diet (Mead Johnson product 3200-A.S., Tables I-III) as the sole source of nutrition for four days before and throughout 5-FU treatment (diet group). The diet group originally comprised 12 patients but three (one man and two women) could not tolerate the taste of the diet and were rejected. The patients in the diet group were allowed water *ad libitum*. This diet was packaged in cans in powder form and served as a liquid by dissolving 370 g. in 1315 ml. of distilled water. This yielded a solution of 1600 ml. with a nutritional value of 1 kcal./ml. The osmolarity at this concentration was 700 mOsm/l. All patients drank the diet cold, one glass at a time often followed by some water, except for two cases (Nos. 5 and 6, Table V), to whom the diet was given, through a gastrostomy, diluted to 500 mOsm/l. In pa-

TABLE I.—3200-A.S. CALORIC DISTRIBUTION

	g./1000 kcal.			*kcal./1000 kcal.*	
Protein equivalent*	24.07	(23.3 min.)		96	
Protein hydrolysate powder		22.94	(22.2 min)		92
Added amino acids		1.13			4
Fat	34.29			304	
Soy oil (lightly hydrogenated)		26.63			240
Medium-chain triglyceride (75% C_8, 25% C_{10})		6.66			55
Lecithin		1.00			9
Carbohydrate	149.93			600	
Corn syrup solids		63.20			253
Sucrose		77.34			309
Arrowroot starch		9.39			38
Product 3200-A.S.	233			(1000)	

* N X 6.25

*Supported by the Medical Research Council of Canada and the Mead Johnson Company of Canada Ltd.

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TABLE II.—3200-A.S. Amino-Acid Content

Amino acid	Free amino acids (g./1000 kcal.)	Added free amino acids (g./1000 kcal.)	Total free amino acids (g./1000 kcal.)	Total amino acids present* (g./1000 kcal.)
Arginine	0.87	—	0.87	0.93
Histidine	0.56	—	0.56	0.70
Isoleucine	1.08	—	1.08	1.42
Leucine	2.22	—	2.22	2.39
Lysine	1.74	—	1.74	2.00
Methionine	0.71	0.75	1.46	1.48
Cystine†	—‡	—	—	0.10
Phenylalanine	0.98	—	0.98	1.12
Tyrosine†	—	0.19	—	0.51
Threonine	0.87	—	0.87	1.09
Tryptophan†	—	0.19	—	0.43
Valine	1.37	—	1.37	1.76
Alanine	0.70	—	0.70	0.84
Aspartic acid	0.49	—	0.49	1.88
Glutamic acid	2.09	—	2.09	5.45
Glycine	0.31	—	0.31	0.56
Proline	1.36	—	1.36	2.53
Serine	1.54	—	1.54	1.48

* Includes amino acids added.
† Determined microbiologically; all others determined with the amino-acid analyzer.
‡ No value available.

tient No. 9 (Table V), who had previous gastrojejunostomy, the osmolarity of the diet was adjusted to 400 to 500 mOsm/l. according to tolerance. The patient's intake of elemental diet was regulated by his own appetite. The diet was prepared in the morning and preserved at 4° C. without contamination for 24 hours; artificial flavour was added to the patient's taste.

TABLE III.—Levels of Vitamins and Minerals in Product 3200-A.S.

	Per 1000 kcal.
Vitamin A, USP units	3125
Vitamin D, USP units	250
Vitamin E, Int. units	18.8
Vitamin C (ascorbic acid), mg.	62.5
Vitamin B_1 (thiamine), mg.	0.9
Vitamin B_2 (riboflavin), mg.	1.1
Vitamin B_6 (pyridoxine), mg.	1.3
Vitamin B_{12}, μg.	3.1
Niacin, mg.	11.3
Folic acid, mg.	0.063
Pantothenic acid, mg.	6.3
Choline, mg.	63
Calcium, mg.	563
Phosphorus, mg.	500
Magnesium, mg.	219
Iron, mg.	6.25
Iodine, μg.	88
Copper, mg.	1.25
Manganese, mg.	3.13
Zinc, mg.	6.25
Sodium, mg.	425
Potassium, mg.	1500
Chloride, mg.	1563

Sigmoidoscopy was performed in all patients on the day after termination of the 5-FU treatment and a rectal biopsy was taken 6 to 7 cm. from the anal orifice. This technique has been employed recently to evaluate the toxic effects of 5-FU on the rectal mucosa, with little risk and no pain to the patient.[2] All specimens were fixed in neutral buffered 10% formalin, processed in an Autotechnicon, embedded in paraffin and sectioned at 5 μ in a plane parallel to the length of the glands. The sections were stained by Harris' hematoxylin and eosin and periodic-acid-Schiff reaction. The height of the surface epithelial cells was measured with a micrometer scale from the base of the cell to the apex. The values reported represent the mean of about 100 surface cells taken at random but excluding the edges of the biopsy. Since the decision to take biopsies in controls was made after the study had begun, the first three control patients were not biopsied. One control and one diet patient refused biopsy. Evaluation of human response to 5-FU was subjective and/or objective over a period of two to eight months. Leukopenia is defined as a leukocyte count below 4000/c.mm. Four cases per group received concomitant cobalt therapy (4000 rads over a period of four weeks) which was started at the same time as the 5-FU.

TABLE IV.—Clinical and Histologic Findings During 5-FU Treatment in Patients on Normal Hospital Food

Patient	Tumour	Age (years)	Sex	Total dose 5-FU (g.)	Concomitant x-ray	Toxicity and symptoms	Tumour response	Mean body weight [1]Before (kg.)	Mean body weight [2]After (kg.)	Mean cal./day during 5-FU	Total serum proteins Before (g./100 ml.)	Total serum proteins After (g./100 ml.)	Mean height of surface epithelium of rectum after 5-FU (μ)
1 SM	Adenocarcinoma of colon	64	M	2.97	no	Diarrhea, leucopenia	Poor	75.5	72.3	—	7.2	6.6	—
2 AR	Adenocarcinoma of stomach	64	M	3.30	—	—	Poor	54.5	50.8	1000	6.1	6.3	—
3 PB	Adenocarcinoma of breast	62	F	3.15	no	—	Good	57.5	54.7	1100	6.9	6.6	—
4 GP	Adenocarcinoma of pancreas	61	M	4.50	yes	Diarrhea, leucopenia	Poor	64.0	61.5	—	7.3	5.6	35.7
5 LO	Squamous carcinoma of esophagus	58	M	2.75	yes	—	Good	44.9	45.6	1782	6.7	6.8	61.2
6 LA	Adenocarcinoma of breast	63	F	3.25	no	—	Fair	—	63.5	—	6.5	6.2	42.5
7 PD	Adenocarcinoma of stomach	53	M	3.60	no	—	Good	—	50.3	—	6.0	5.8	39.1
8 NP	Oat-cell carcinoma of lung	55	M	4.00	yes	—	Excellent	59.0	58.4	2822	6.9	6.6	42.5
9 RC	Adenocarcinoma of colon	55	M	5.25	no	—	Excellent	76.4	68.9	1533	6.5	6.9	—
10 AC	Adenocarcinoma of colon	58	M	5.25	yes	—	Good	61.1	59.9	1913	6.8	7.0	39.1
11 GB	Adenocarcinoma of stomach	46	M	4.50	no	Leucopenia	Poor	66.1	60.6	—	7.0	6.2	37.4
12 YP	Adenocarcinoma of rectum	68	F	3.35	no	—	—	53.8	52.4	1326	6.6	7.4	39.5
Mean:		58.8		3.82	—	—	—	61.2	58.1	1639	6.7	6.5	42.1

(1) Mean during the days before 5-FU.
(2) Mean of last three days on 5-FU.

Statistical Analysis

In the computation of body weight, the mean of the values obtained on different days during the eight days preceding 5-FU was compared to the mean of the values obtained during the last three days of treatment by a one-sample t test for both groups.

Results

Clinical Findings

The age, sex, diagnoses, total dose of 5-FU, toxicity symptoms, caloric intake and body weights of these 21 patients are recorded in Tables IV and V.

At the end of 5-FU treatment, the average loss of body weight of patients in the control group was 2.77 kg. ($P < 0.01$) (Table IV). In contrast, patients on the elemental diet maintained their weight in spite of the 5-FU therapy. Total caloric intake, measured during treatment, appeared to be about the same whether the patient

TABLE V.—Clinical and Histologic Findings During 5-FU Treatment in Patients on Elemental Diet 3200-A.S. (Mead Johnson)

Patient	Tumour	Age (years)	Sex	Total dose 5-FU (g.)	Concomitant x-ray	Toxicity and symptoms	Tumour response	Mean body weight [1]Before (kg.)	Mean body weight [2]After (kg.)	Mean cal./day during 5-FU	Total serum proteins Before (g./100 ml.)	Total serum proteins After (g./100 ml.)	Mean height of surface epithelium of rectum after 5-FU (μ)
1 RD	Squamous carcinoma of lung	55	M	2.50	yes	—	Good	54.5	54.5	2200	7.0	7.0	56.1
2 RF	Adenocarcinoma of colon	55	M	3.50	yes	Leucopenia	Good	56.5	55.2	2100	6.9	6.8	59.5
3 RG	Adenocarcinoma of pancreas	45	M	3.90	yes	Leucopenia	Excellent	42.0	41.8	2360	6.5	6.1	—
4 LD	Adenocarcinoma of stomach	57	M	4.42	no	Leucopenia	Poor	42.1	42.2	1000	5.7	5.5	52.7
5 OL	Squamous carcinoma of pharynx	68	F	4.42	yes	—	Poor	68.1	68.2	1600	7.2	7.1	52.7
6 TF	Squamous carcinoma of pharynx	54	M	4.20	no	—	Poor	59.8	58.0	1600	5.3	5.6	76.5
7 NR	Adenocarcinoma of gallbladder	65	F	4.50	no	—	Poor	82.9	84.9	1200	6.8	6.5	51.0
8 HC	Adenocarcinoma of stomach	62	M	4.15	no	—	Good	59.1	60.7	2100	6.4	6.3	66.0
9 AL	Adenocarcinoma of stomach	62	M	4.55	no	—	Good	51.8	51.8	1254	6.3	6.2	50.0
Mean:		58.1		4.01	—	—	—	57.4	57.4	1725	6.5	6.3	58.1

(1) Mean during the days before 5-FU.
(2) Mean of last three days on 5-FU.

ate normal food or the elemental diet. However, when caloric intake is expressed per kilogram body weight, we observed a difference between the two groups: controls took 20.4 kcal./kg. and diet patients 27.1 kcal./kg. Serum lactic dehydrogenase, alkaline phosphatase, bilirubin, cholesterol, glucose and protein were not statistically different in the two groups.

Histologic Findings

The crypt epithelium of control patients showed varying degrees of karyorrhexis, karyiolysis and loss of nuclear polarity. Sometimes a mass of desquamated cells was visible in the luminal side of the crypt. The numbers of goblet cells and mitoses were decreased. Only two patients (Nos. 4 and 11, Table IV) showed severe atrophy of the mucosal glands (Figs. 1 and 3). The patients on the diet had similar lesions in the crypts, although the cellular desquamation was less evident and there was no glandular atrophy.

In the surface epithelium, the difference between the two groups was more striking. In controls (Figs. 1, 3, 5 and 7) we observed a diminution of mucin; the cells were shorter, sometimes cuboidal or flattened with vacuolization of the basal part of the cytoplasm. The photographic series, particularly those at low power, clearly indicate that the epithelial cells are better preserved in the diet group: they have more mucin, less vacuoles, dense cytoplasm and taller cells (Figs. 2, 4, 6 and 8). The mean height of the surface rectal epithelium was 42.1 μ in the control group and 58.1 μ in the diet group ($P < 0.01$) (Tables IV and V).

Discussion

Our observations in man agree with those of previous investigators who demonstrated histologic abnormalities in human colonic and rectal mucosa following parenteral administration of 5-FU.[2, 3] With one exception (No. 5, Table IV) all biopsies in the control group showed significant histologic changes. In this study, the total cumulative dose of 5-FU never exceeded 5.25 g.: this dose is significantly less than in most of the patients studied by Floch and Hellman[2] who reported diarrhea in all cases. This probably explains why we saw diarrhea in only two patients and found somewhat different rectal lesions. We have seen pyknosis, nuclear debris and loss of polarity in the crypts, but a quantitative comparison of these parameters is difficult. An objective evaluation of the lesions can be made in the surface epithelium if extreme care is taken in processing the sample. By visualizing the cell membrane at the base and in the area surrounding the mucin at the apex, it was possible to assess the cell in its entirety for comparative studies. Our low-power photographs represent the middle portion of the biopsy—the major part of the excised tissue. The difference between patients on regular hospital food and those on the elemental diet was striking. The surface epithelium of the rectum was normal in all the patients we examined in the diet group with the possible exception of patient No. 2 (Table V). Only one control patient examined (No. 5, Table IV) presented a normal histologic pattern.

In rats treated with 5-FU and taking a normal diet, we observed rectal lesions comparable to the ones seen in our control patients. These lesions were always associated with severe necrotic changes in the mucosa of the ileum and jejunum.[1] If we extrapolate these findings to the human condition, we can assume that the absorbing cells of the human small intestine suffer some damage after 5-FU administration. In the rat, the mucosa of the upper intestine and the mucosa of the rectum are protected equally by an elemental diet; it is thus possible that the beneficial effects exerted by the diet in the lower intestine of our patients extend to the mucosa of the upper intestine. We are further justified in this assumption by the behaviour of the body weight: our diet group lost almost no weight during 5-FU treatment but the controls had significant weight loss. One apparent exception that does not appear in Table V is patient No. 9 who ate the diet for 12 days but almost completely stopped eating during the last three days because the taste had become

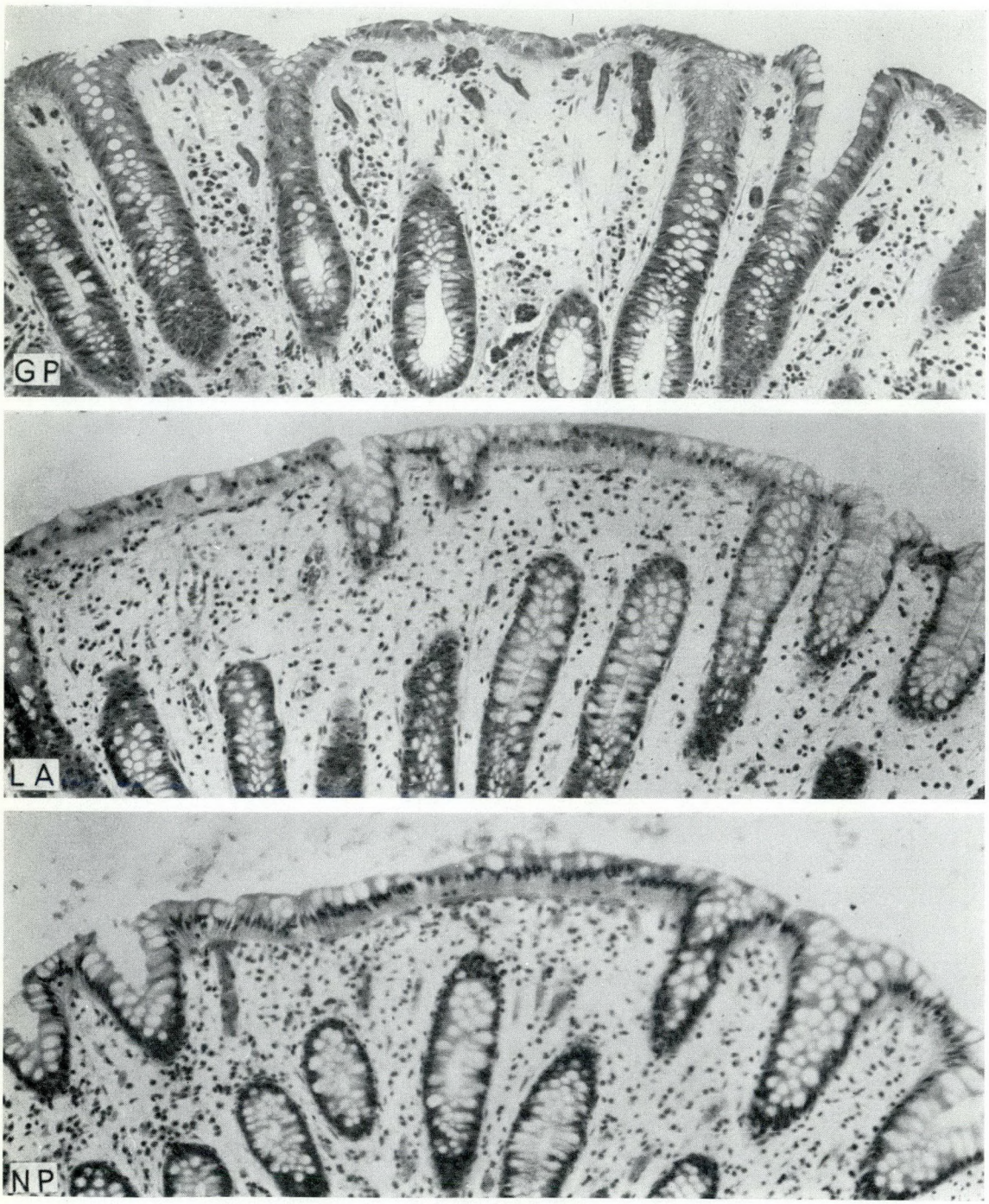

Fig. 1.—Rectal biopsies of patients on normal hospital food at the end of 5-FU treatment. Microscopic sections show a certain degree of glandular atrophy, necrotic and flattened surface epithelium with loss of goblet cells (patient GP), and shorter surface epithelium with decreased mucin (patients LA and NP) (H & E × 140).

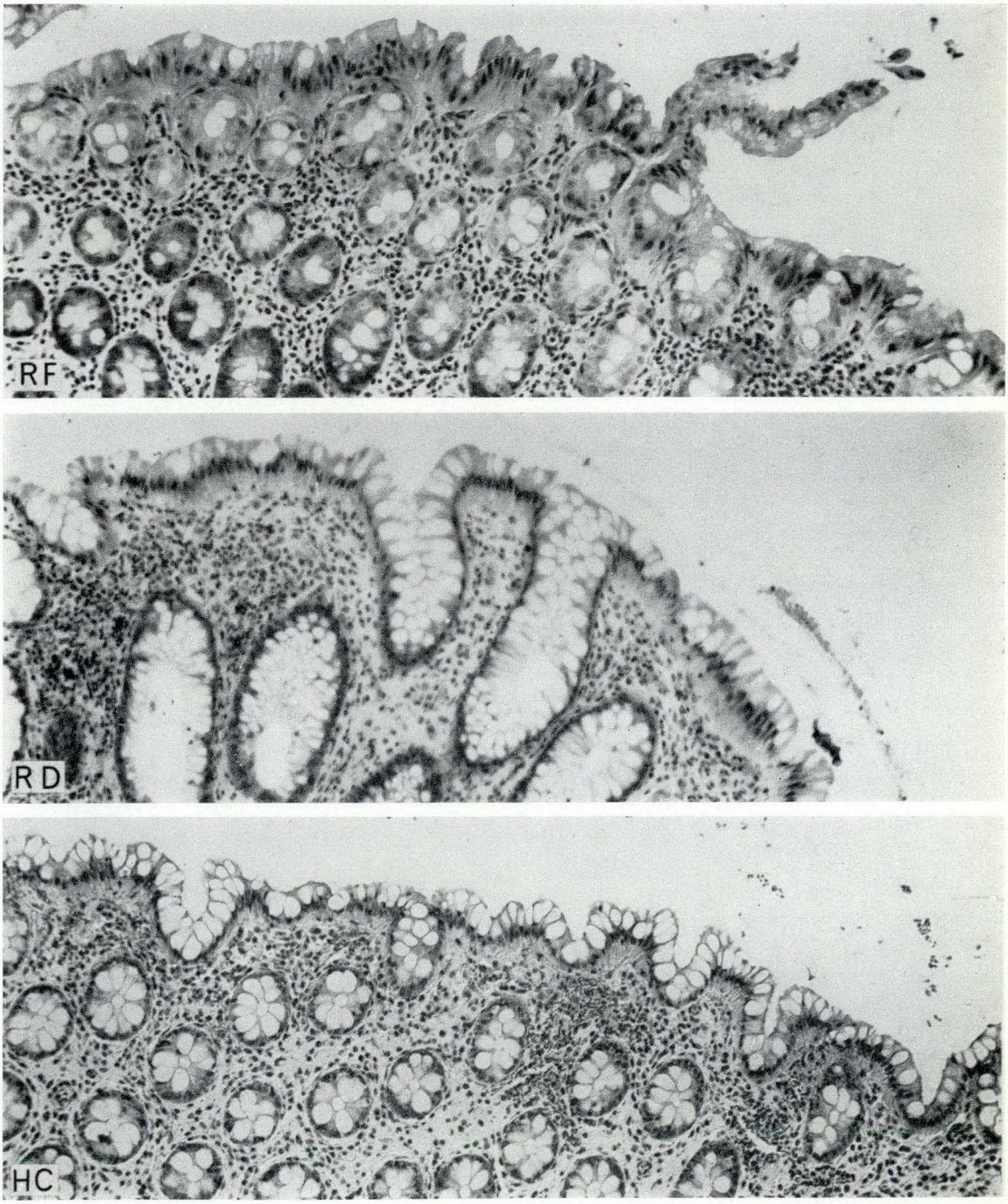

Fig. 2.—Rectal biopsies of patients RF, RD and HC on an elemental diet at the end of 5-FU treatment. Microscopic sections show normal mucosa (H & E × 140).

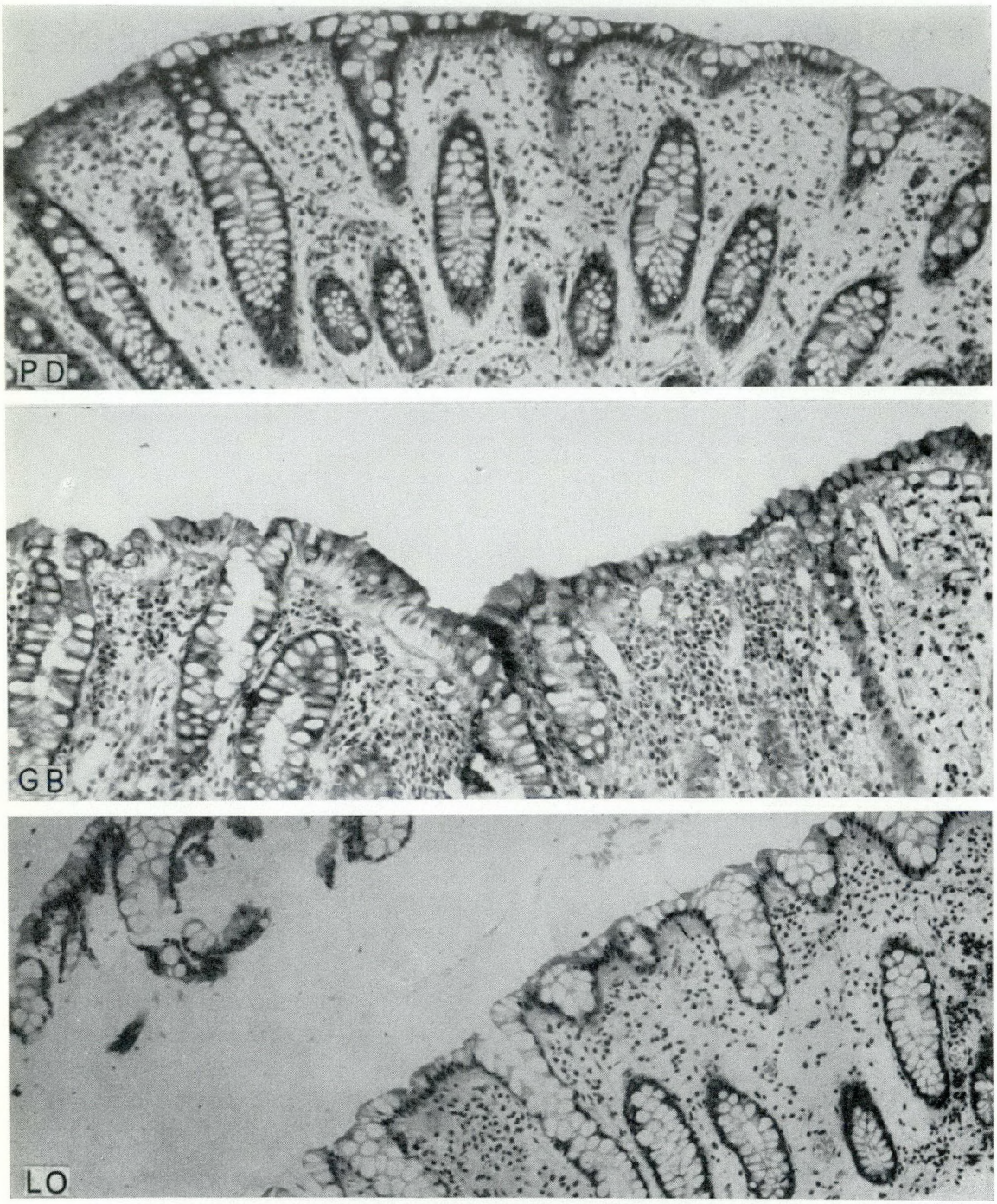

Fig. 3.—Rectal biopsies of patients on normal hospital food at the end of 5-FU treatment. Microscopic sections show shorter surface epithelium with vacuolization in the basal part of the cell (PD and GB), some glandular atrophy (GB) and normal mucosa (LO) (H & E × 140).

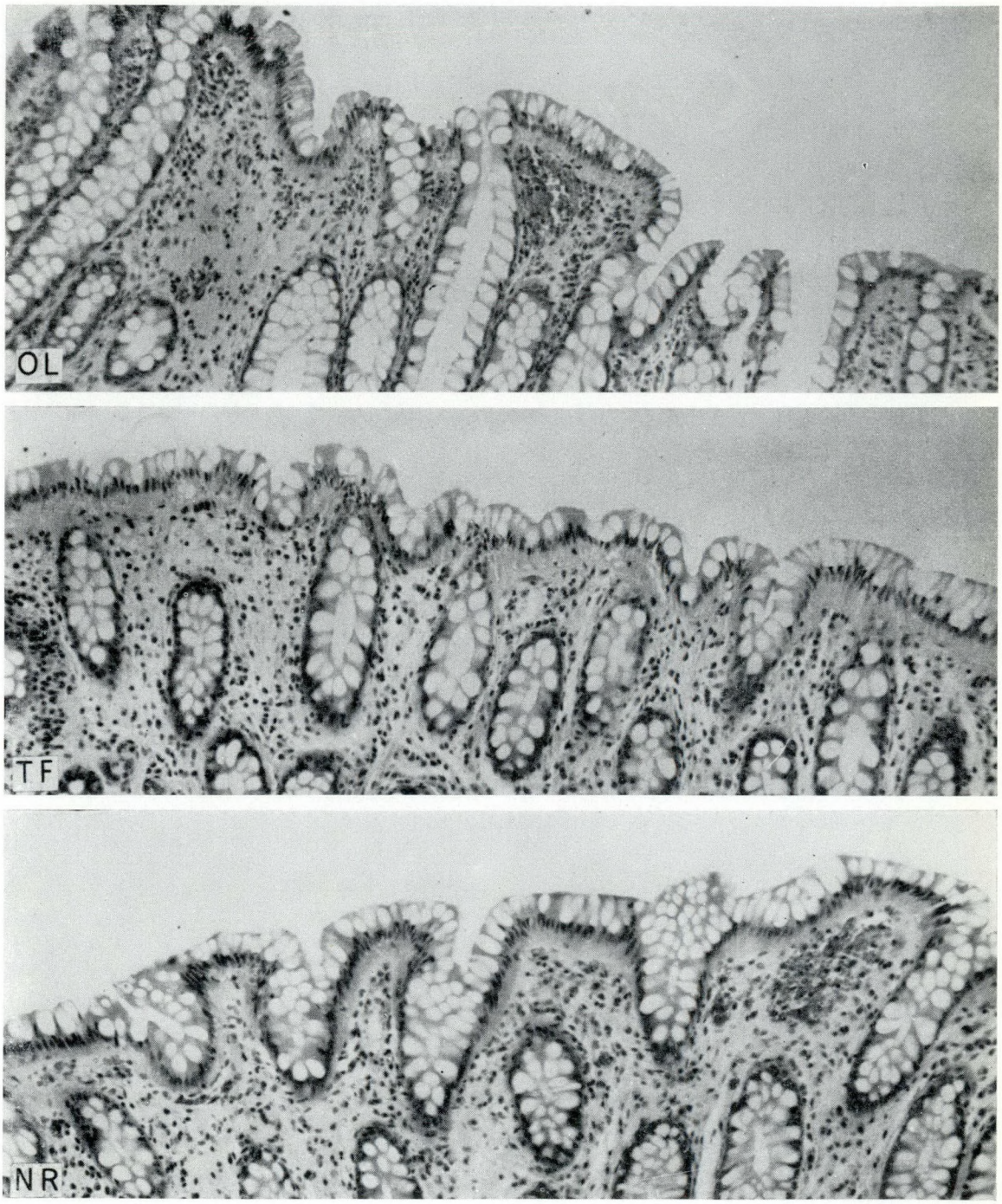

Fig. 4.—Rectal biopsies of patients OL, TF and NR on the elemental diet at the end of 5-FU treatment show normal mucosa (H & E × 140).

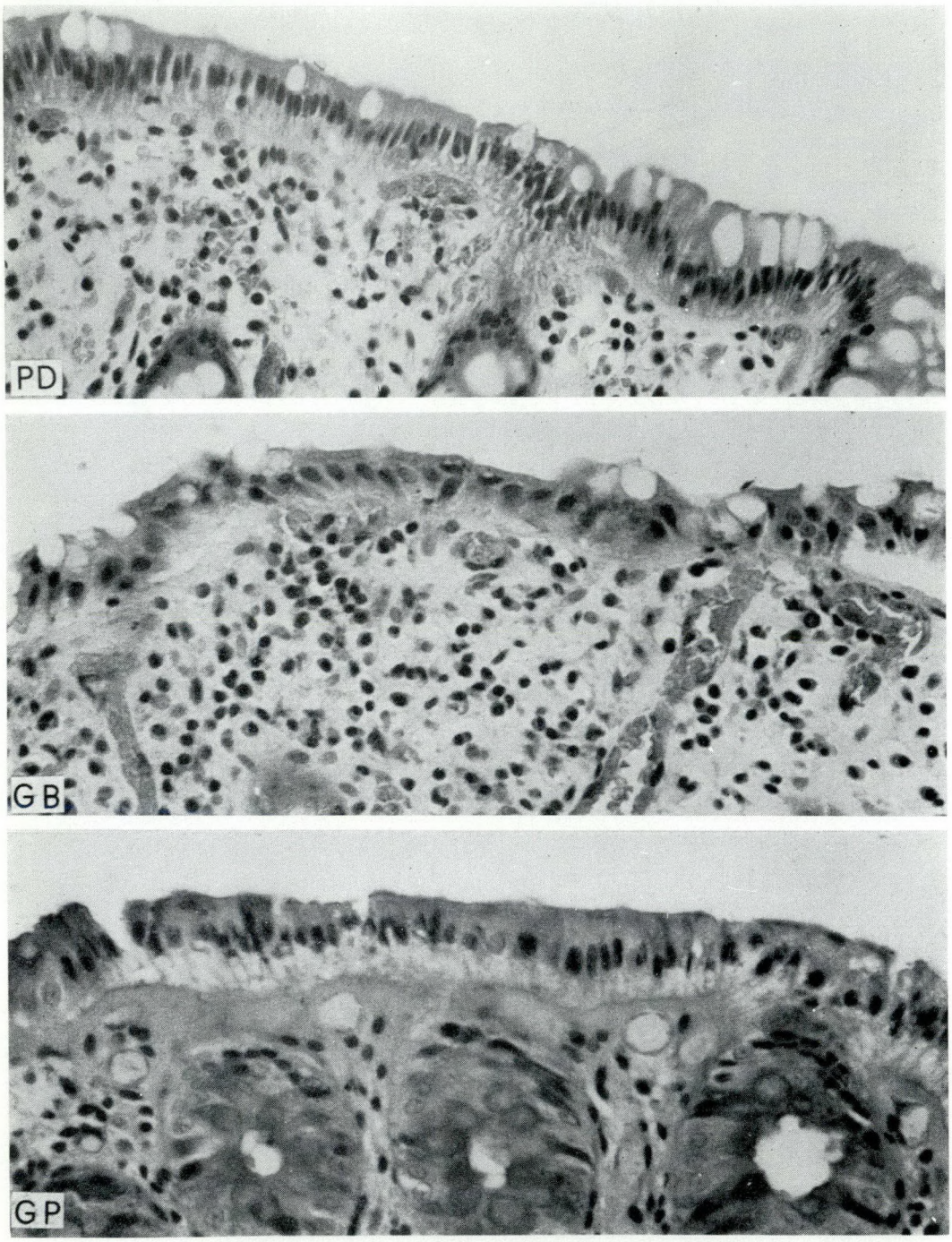

Fig. 5—High-power details of biopsies from patients PD, GB and GP on normal hospital food showing vacuolization and loss of mucin in the surface epithelium (H & E × 352).

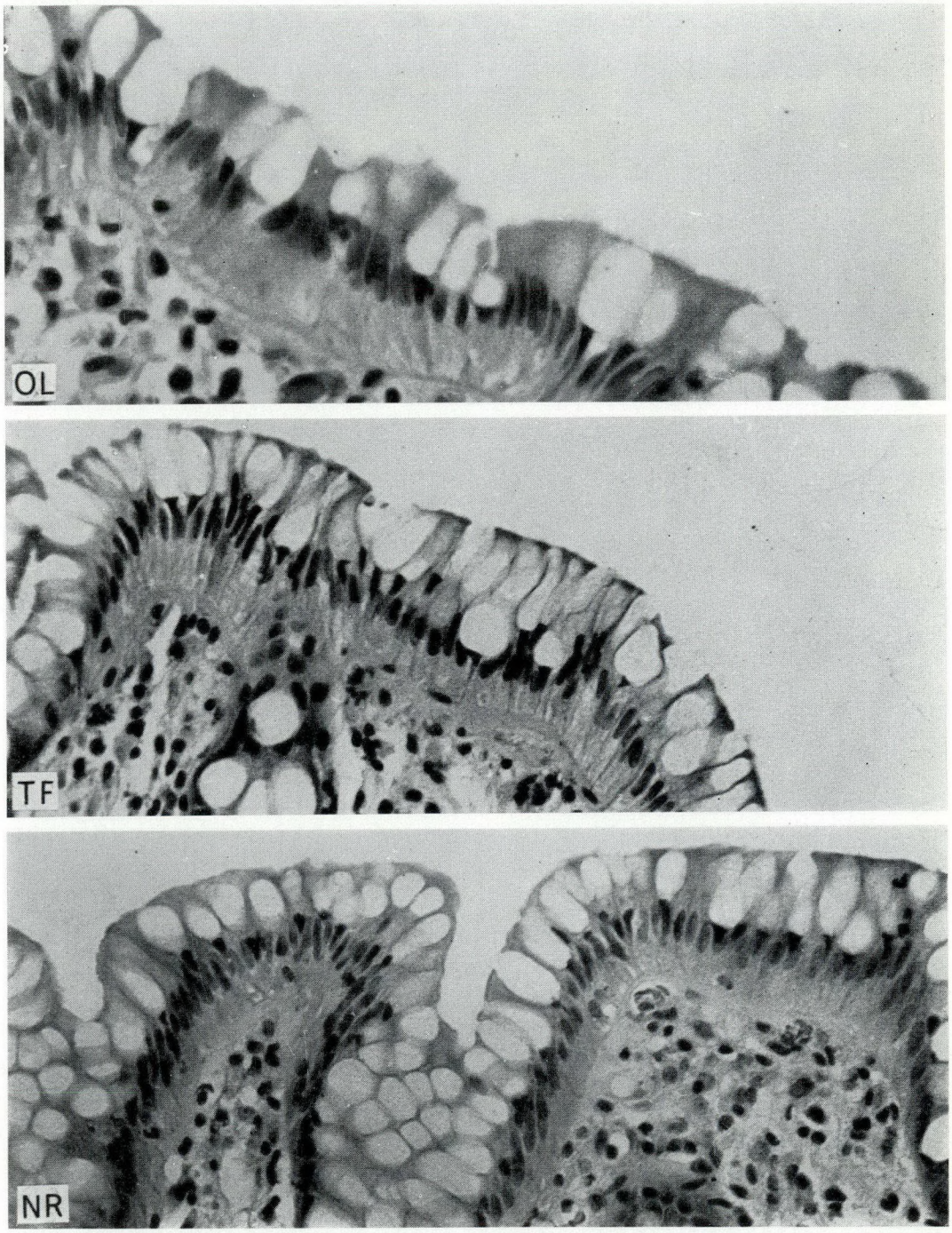

Fig. 6.—High-power details of biopsies shown in Fig. 4 (patients OL, TF and NR) showing normal surface epithelium (H & E × 352).

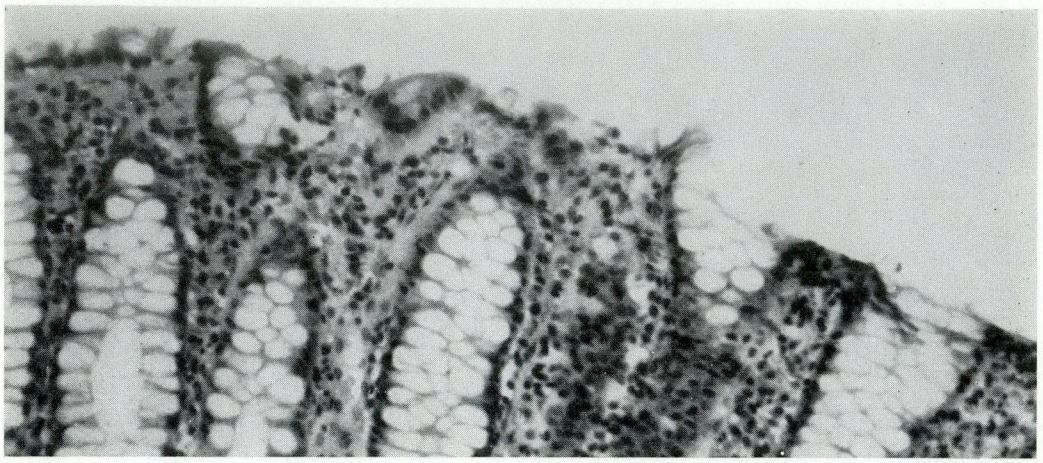

Fig. 7.—Rectal biopsy of a patient (YP) eating normal hospital food at the end of 5-FU treatment. The section shows a flattened necrotic surface epithelium (H & E × 140).

intolerable. For this reason we excluded these last three days in making the calculations shown in Table V.

The elemental diet contains no added bulk or indigestible material. Consequently, the stools of the subjects have a smaller bulk and a different appearance, colour and consistency from stools that result from the ingestion of normal foodstuffs. The occasional watery and loose stools do not constitute diarrhea, since the total amount of water eliminated is substantially less than that eliminated on a natural foodstuff diet.

The relative concentration of hydrolyzed proteins in the elemental diet for man is around 10% as compared with 20% in the diet for rats.[1] The concentration of amino acids in the diet 3200-A.S. for humans is the result of a compromise between palatability and daily minimal nitrogen requirement as established for man by the Food and Nutrition Board of the National Academy of Sciences.[4] According to their 1968 report, the recommended dietary allowance for a 70-kg. man is equivalent to 34 g. of protein with a biologic value of 100, i.e. the nitrogen is totally used; this

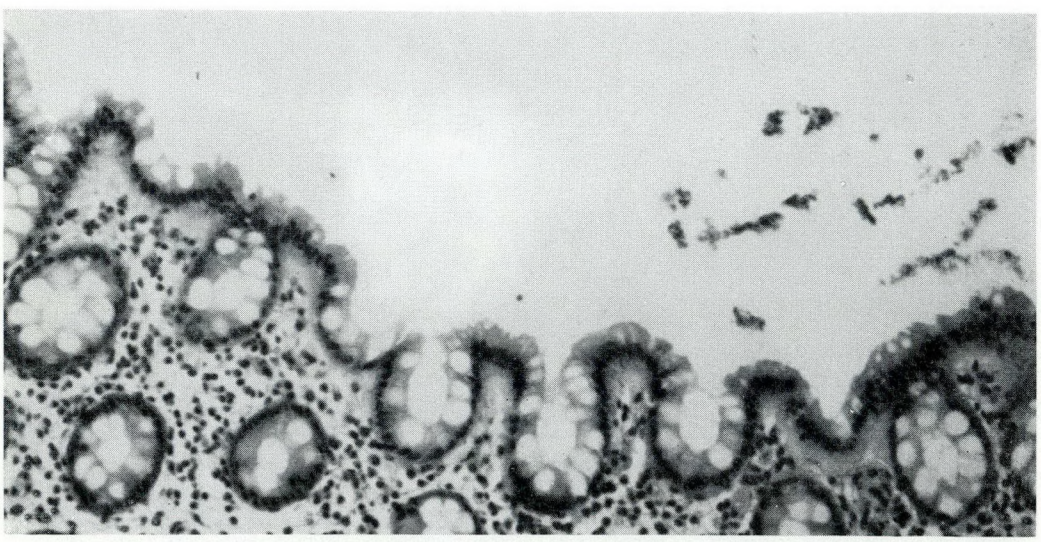

Fig. 8.—Rectal biopsy of a patient (AL) eating the elemental diet at the end of 5-FU treatment. The section shows a normal mucosa (H & E × 140).

would represent a protein requirement of 20 mg./basal kcal. Moreover, the jejunal mucosa of man has been shown to tolerate protein starvation far better than the mucosa of rats.[5] For all the aforementioned reasons, the diet 3200-A.S. was effective in protecting the human mucosa despite a concentration of nitrogen inferior to the values in the rat diet.[1]

In our experimental work we demonstrated that the protection afforded by an elemental diet depended specifically upon the amino acids substituted for whole protein. This conclusion was reached by using as control diets not only regular animal food but also a replica of the elemental diet in which the casein hydrolysate had been replaced by whole casein. Although in our clinical study such a refined control diet was not used, it is likely that here too the amino acids are responsible for the protective effect. The paper describing our experimental work[1] enumerated several ways in which an elemental diet may be beneficial. An important factor was recognized when we discovered that, 24 hours after 5-FU, dipeptidase activity dropped sharply in the absorbing cells that are still anatomically intact, while other hydrolases are actually activated.[1] We postulated that, in the face of such a severe inhibition of the terminal digestion of proteins, an amino-acid diet would meet more effectively the nutritional and biosynthetic requirements of the epithelium lining the mucosa. Probably a similar mechanism operates in the human intestine.

During administration of 5-FU, the average total caloric intake was about the same in the two groups of patients (Tables IV and V) although when expressed per kilogram of body weight it appeared somewhat higher in the diet group. In the rat, we found no significant difference in caloric intake between diet and control animals following 5-FU. The healthier appearance of the ileal mucosa also suggested a better utilization of ingested food. Conceivably we had an analogous situation in our clinical series, although the effects of 5-FU were less severe in all parameters studied.

The object of the study was not to investigate the response of the tumour to 5-FU but the toxicity of this cytostatic agent on the intestinal mucosa and hence on nutrition. Our results indicate that an elemental diet confers a dual benefit: it protects mucosal integrity and increases the absorption of essential elements, i.e. amino acids. It is reasonable to propose that the resulting improved nutrition can assist the body's defence against the disease process.

Summary

In patients eating a normal hospital diet, palliative treatment of advanced metastatic carcinoma is associated with significant weight loss and specific lesions of the rectal mucosa. A comparable group of patients eating a hydrolyzed elemental diet (Mead Johnson 3200-A.S.) four days before and throughout the six to nine days of 5-FU treatment had no rectal lesions and maintained their pretreatment body weight.

Earlier experimental work in rats with a similar elemental diet suggested that several factors contribute to this protection. Some of them have their effect by altering the intestinal *milieu* before injury; others seem to operate in the phase after injury. Soon after 5-FU injection, we found that dipeptidase activity dropped to very low levels and presumably the terminal digestion of proteins was severely impaired. In these experiments it was clear that the protection offered by the elemental diet depended on the substitution of amino acids for whole protein.

The authors wish to thank Mr. Jacques Payeur, medical student at the University of Sherbrooke, for helping to collect the data; Miss Lucille Letourneau, head nurse, for intelligent co-operation in the care of the patients; and Misses Renée Bachand and Pauline Carrier, dieticians. The technical and scientific assistance of Dr. J. E. Knapp, of the Mead Johnson Company of Canada Ltd., is gratefully acknowledged. We thank Dr. B. J. Perey, Chairman, Department of Surgery, University of Sherbrooke for reviewing the manuscript.

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RÉSUMÉ

Le traitement palliatif du cancer avancé avec le 5-FU engendre une perte significative de poids et des lésions spécifiques de la muqueuse rectale. Un groupe de patients se nourissant d'une diète élémentaire hydrolisée (Mead Johnson 3200-AS) pendant quatre jours avant et durant les six à neuf jours d'administration de 5-FU n'a pas présenté de lésion rectale, ni de perte de poids. Nos travaux experimentaux antérieurs chez le rat prenant une diète semblable ont montré que plusieurs facteurs contribuent à ce mécanisme de protection. Certains d'entre eux agissent avant la chimiothérapie en modifiant le milieu intestinal alors que d'autres semblent agir durant la phase de traitement. Nous avons constaté que peu après l'injection de 5-FU, l'activité des dipeptidases dans les cellules intestinales tombe à un niveau très bas de façon à compromettre la digestion terminale des protéines et par là, leur utilisation. Il paraît évident que la protection offerte par la diète élémentaire est reliée à la présence d'acides aminés remplaçant les protéines.

MAJOR ABDOMINAL SURGERY IN THE ELDERLY: A REVIEW OF 172 CONSECUTIVE PATIENTS*

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MOST North Americans will continue to live for increasingly longer periods of time. If the present trend continues, by 1980 one person in every five will be 70 years of age or over. As a result, the general surgeon is required, with increasing frequency, to operate upon persons in this age group.

The surgical management of the elderly, like the very young, presents challenging problems. For this reason, we reviewed 200 unselected consecutive cases of major abdominal surgery in 172 patients over 70 years of age operated on at the Ottawa General Hospital between May 1966 and June 1969. Of the 172 patients in the study, 72 were men and 100 women, with an age range of 70 to 90 years and a mean of 76 years.

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PRIMARY DISEASES

The primary diseases leading to operation were many and varied but fell into several large groups including benign biliary tract disease (41%) and colorectal malignancy (22%) (Table I).

TABLE I.—PRIMARY DISEASES IN 172 PATIENTS

	No. of patients	*Percentage of total*
Benign biliary tract	70	41
Other benign	57	33
Colorectal malignancies	37	22
Other malignancies	8	4
Total	172	100

Of the 70 patients with biliary tract disease, 56 had chronic cholecystitis and 15 (27%) of these had stones in the common bile duct (Table II). Nine patients had acute cholecystitis, two had empyema of the gallbladder, two had choledochoduodenal fistula and one had a stricture of the common duct.

TABLE II.—Benign Biliary Tract Diseases in 70 Patients

	No. of patients
Chronic cholecystitis and cholelithiasis	41
Chronic cholecystitis and choledocholithiasis	15
Acute cholecystitis	9
Empyema of gallbladder	2
Choledochoduodenal fistula	2
Stricture of common bile duct	1
Total	70

Of 45 patients with malignant disease, 37 had tumours of the colon or rectum (Table III). Other primary sites included

TABLE III.—Site of Malignancies

	No. of patients
Colorectal	37
Stomach	2
Gallbladder	2
Jejunum	1
Ileum	1
Pancreas	1
Liver	1
Total	45

the stomach, gallbladder, small bowel, pancreas and liver. This series reflects the usual distribution of colon cancer. Nearly two-thirds of the colorectal malignancies were in either rectum or sigmoid (Table IV).

TABLE IV.—Site of Colorectal Malignancies

	No. of patients
Cecum	2
Ascending colon	5
Hepatic flexure	1
Transverse colon	4
Splenic flexure	3
Descending colon	1
Sigmoid colon	15
Rectum	6
Total	37

Associated Diseases

One hundred and forty-three patients (83% of the total) had significant associated disease; 114 had cardiac disease manifested clinically or through an electrocardiographic abnormality. More than one-quarter of the total (47 patients) had chronic chest disease.

Anemia (defined as a hematocrit of less than 35%) was present in 32 patients, symptomatic cerebrovascular disease in 26 and peripheral vascular disease in 18. Sixteen patients were diabetic; 10 were treated with oral hypoglycemic agents and six with insulin. Many patients had more than one significant associated disease.

Operative Procedures

The operations were elective in 75% of patients and emergency in 25% (Table V).

TABLE V.—Operative Procedures (Elective 75%, Emergency 25%)

		No. of operations	*Percentage of total*
Gastrointestinal resection		74	37
Colon	52		
Stomach	12		
Small bowel	10		
Benign biliary tract		70	35
Others		56	28
Total		200	100

Resection of some part of the gastrointestinal tract was done during 74 procedures, 37% of the total. Of these, 52 operations were colon resections, 10 small-bowel resections and 12 gastrectomies.

Of 70 cholecystectomies, the common duct was explored in 27 and stones were recovered in 15. Cholecystectomy was combined with resection of the choledochoduodenal fistula in two procedures and a choledochoplasty in one.

Complications

Thirty-five per cent of patients had significant postoperative complications; a single patient often had more than one. The most common were pulmonary and occurred in 37 patients; 17 developed atelectasis, 12 pneumonia and eight pulmonary embolism. Twenty-two patients had wound complications; of these 16 had wound infections and six had dehiscences.

After gastrointestinal resection, the anastomosis leaked on 13 occasions, i.e. after 18% of resections. Eleven patients developed urinary complications; seven had infection and four retention. Eight patients had recognized cardiac complications, infarction in five and significant arrhythmia in three.

The average hospital stay of survivors was long, 30.9 days, largely due to pro-

longed preoperative investigation, a higher incidence of complications, and difficulty in finding suitable accommodation after recovery.

Mortality

Nineteen of these 172 patients died—an operative mortality of 9.5% or a patient mortality of 11% (Table VI). Seven died after elective operations and 12 after emergency surgery.

Subtotal gastrectomy was tolerated poorly; of the 12 patients who had this procedure, four died. Three of these died after emergency gastrectomy for uncontrolled massive upper gastrointestinal hemorrhage. The mortality rate for colon resection was 13.5% and operations on the biliary tract 4.3%.

TABLE VI.—Operative Mortality

	No. of procedures	*No. of deaths*	*Percentage*
Emergency	50	12	24.0
Elective	150	7	4.7
Total	200	19	9.5

The commonest cause of death was respiratory infection or failure. Twelve patients (63%) died from respiratory causes; seven from pneumonia, four from pulmonary embolism and one from massive atelectasis. Cardiac complications claimed four lives (21%). Three patients (16%) died from peritonitis secondary to anastomotic leak after gastric or colon resection.

Discussion

In itself advanced age is not a barrier to successful surgical treatment. From this review of 172 consecutive patients, certain points emerge which are not new but which merit further consideration.

From the standpoint of malignant disease, 37 of 45 malignancies involved the colon or rectum. The infrequent involvement of other parts of the gastrointestinal tract, in particular the stomach, was surprising. In this series, carcinoma of the stomach was no more common than carcinoma of the gallbladder—a finding that seems to support the apparent decrease in carcinoma of the stomach reported on this continent in recent years.

The distribution of colorectal cancer was in keeping with that reported in other series; almost two-thirds occurred in the rectum or sigmoid. Hence, the routine proctosigmoidoscopy of all patients in this age group with or without symptoms should be a part of every complete physical examination.

Almost all these patients had significant associated disease, in particular arteriosclerotic heart disease and chronic chest disease were common. According to Bosch *et al.*,[1] the mortality of patients in this age group undergoing surgery is twice as high in those with significant concurrent disease as in those without associated disease. They stress the importance of close cooperation between surgeon and internist in the preoperative care of elderly persons. In this study, we requested medical consultation for cardiopulmonary assessment in almost all patients—a practice justified by the high incidence of associated coronary artery disease. The discovery of significant associated disease before operation will identify the patient who is likely to develop such complications as postoperative pneumonia, pulmonary embolism or fatal arrhythmia.

It has long been taught that elderly patients tolerate prolonged operations poorly. However, we were unable to demonstrate any relationship between duration of anesthesia and incidence of postoperative complications or mortality. This suggests that a hurried procedure is not justified and that time devoted to obtaining adequate exposure and hemostasis is well spent.

The postoperative complication rate (35%) was high, but not surprising if one remembers that 83% of the patients had associated diseases. As in other series, pulmonary complications caused the greatest morbidity and mortality. More liberal use of pulmonary function studies might help to identify those who need intensive preoperative physiotherapy or postoperative ventilatory assistance. We would like to stress the importance of early activity as opposed to early ambulation. A seriously ill elderly patient, convalescing from a

major operation derives little, if any, benefit from the bed-chair regimen usually prescribed. Such patients are better kept in bed, encouraged to cough, breathe deeply and actively exercise their limbs rather than being forced into early ambulation.

The overall operative mortality rate (9.5%) seems high but is lower than that reported elsewhere for patients over 70 years of age.[2, 3] This figure is about three times higher than that for all major abdominal operations for all ages. As in other series, the elderly seemed to tolerate elective surgery well but emergency procedures poorly; the respective mortality rates are 4.7% and 24%. The increase in mortality rate after emergency procedures seems to be due chiefly to inadequate preparation of these seriously ill patients for what are often major procedures. In particular, subtotal gastrectomy for massive upper gastrointestinal bleeding was poorly tolerated and a lesser procedure should be substituted when possible.

Although 114 patients had associated cardiac disease, only four died from cardiac causes. In this series, the criteria for diagnosis of ischemic heart disease were liberal, and some patients had only nonspecific electrocardiographic changes. In those patients with potential arrhythmias, continuous postoperative monitoring detected arrhythmias early and they were suppressed with appropriate medication before potentially fatal arrhythmias could develop.

Summary and Conclusions

At the Ottawa General Hospital, between May 1966 and June 1969, 200 consecutive major abdominal procedures were performed on 172 patients over 70 years of age. The commonest primary diseases were benign disease of the biliary tract and colorectal malignancies. Significant major associated diseases were almost universal and, when time is available, they should be carefully sought. Postoperative complications were common and most often affected the lungs. Cardiac complications were uncommon in spite of the high incidence of associated heart disease. The overall operative mortality rate was 9.5%. The patients tolerated elective procedures well, but the mortality following emergency operations was high. Of the 12 patients who had subtotal gastrectomy, four died. The commonest cause of death was pulmonary infection or failure.

Pulmonary complications and mortality can be reduced by more liberal use of pulmonary function studies, and greater attention preoperatively to the improvement of pulmonary function.

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Résumé

A l'Hôpital Général d'Ottawa (Ottawa, Ont.) de mai 1966 à juin 1969, 200 opérations abdominales majeures consecutives ont été pratiquées sur 172 patients de plus de 70 ans. Les pathologies primaires les plus courantes portaient sur des maladies bénignes des voies biliaires et des tumeurs malignes du côlon et du rectum. Une pathologie importante connexe était quasi universelle et, quand on dispose du temps voulu, elle devrait être recherchée avec attention. Les complications postopératoires étaient fréquentes et, dans la majorité des cas, affectaient les poumons. Les complications cardiaques ont été rares, malgré la fréquence élevée des cardiopathies connexes. Le taux de mortalité globale a été de 9.5%. Les interventions électives ont été bien tolérées, mais la mortalité consécutive à une opération d'urgence était élevée. Sur 12 patients qui avaient dû subir une gastrectomie subtotale, quatre ont décédé. La cause de décès la plus fréquente a été l'infection ou l'insuffisance pulmonaire. On pourait réduire les complications et la mortalité par une étude plus approfondie de la fonction pulmonaire et par une amélioration pré-opératoire de la dite fonction.

TONE OF THE GASTROESOPHAGEAL JUNCTION: ITS RESPONSE TO ABDOMINAL COMPRESSION AND TO SWALLOWING*

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At the gastroesophageal junction, a high pressure zone (HPZ) separates the intraluminal gastric pressure from the intraluminal esophageal pressure.[1] This zone was previously called the gastroesophageal sphincter; however, because there is no demonstrable anatomical sphincter, the term "high pressure zone" (HPZ) is now commonly used to describe this pressure barrier. The HPZ has been extensively studied anatomically and physiologically because it is believed to be one of the chief barriers to the reflux of gastric contents into the esophagus.

In the normal subject,[2-4] the HPZ is approximately 4 cm. long and straddles the diaphragmatic hiatus (Fig. 1). Because it is partly below and partly above the diaphragmatic hiatus, it is exposed to intra-abdominal pressures at its distal end, and intrathoracic pressures at its proximal end. At the distal end, the intra-abdominal pressure exerts two effects: firstly, being higher than intrathoracic pressure, it produces an elevation of intraluminal HPZ pressure; secondly, with inspiration, intra-abdominal pressure increases and produces positive respiratory deflections in the distal HPZ (G+E). The proximal HPZ is exposed to the lower pressure of the intrathoracic cavity and, consequently, the intraluminal pressure is lower in this area. Within the thoracic esophageal lumen, pressure changes with respiration will be inspiratory negative owing to the negative inspiratory pleural pressures. The point at which inspiratory positive pressure changes to inspiratory negative pressure is referred to as "the point of respiratory reversal" (PRR). This is the physiologic point where the balance of forces changes the respiratory deflection from positive to negative. In the normal subject, this point lies close to the anatomical diaphragm. In patients with a hiatus hernia, the PRR often lies proximal to the anatomical diaphragm. The significance of this variation will be discussed later. During endoscopy under local anesthesia, this point can be clearly seen; above it, the esophagus tends to open with inspiration.

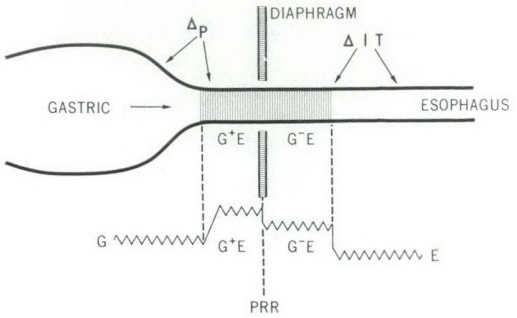

Fig. 1.—The physiologic HPZ straddles the gastroesophageal junction in the normal subject. The distal HPZ, because it lies in the abdominal cavity, is exposed to the inspiratory positive pressures generated by the descent of the diaphragm in respiration. Gastric and peritoneal pressures are inspiratory positive and the distal HPZ is also inspiratory positive. In the normal subject the proximal HPZ is in the thoracic cavity, and is exposed to the respiratory negative inspiratory pressures generated by the descent of the diaphragm and general enlargement of the intrathoracic volume by rib-cage expansion. Therefore, the proximal HPZ and the body of the esophagus show inspiratory negative pressure waves with respiration. The point of change in the HPZ from inspiratory positive to inspiratory negative is referred to as the point of respiratory reversal (PRR). In the normal subject, the PRR lies at or close to the anatomical diaphragm. In subjects with a hiatus hernia, the PRR does not necessarily lie at the anatomical diaphragm. P = peritoneal pressure; IT = intrathoracic pressure; G+E = respiratory positive HPZ; G-E = respiratory negative HPZ; G = gastric pressure; E = esophageal pressure.

Because of the importance of the HPZ, its properties should be measured in a reproducible manner so that we can compare the pressure in this zone in normal and abnormal states. At the present time, the most commonly measured pressure in this zone is the total intraluminal pressure,

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which is recorded while withdrawing a sensor through the zone. This total pressure can be regarded as the intrinsic tone of the HPZ muscle (Fig. 2) as modified by

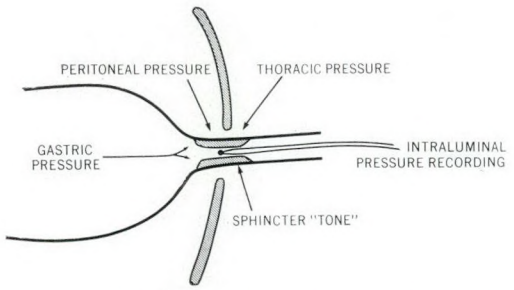

Fig. 2.—The HPZ (sphincter area) at the gastroesophageal junction has an intrinsic pressure or tone, which is the force maintained by the esophageal muscle of this zone. Surrounding pressures, however, affect the intraluminal esophageal pressure as recorded by a pressure recording device in the HPZ: in the abdomen these are the peritoneal and gastric pressures and in the thorax, the esophageal and intrathoracic pressures.

the gastric, peritoneal and intrathoracic pressures. Hence, because gastric, peritoneal and intrathoracic pressures vary, so also must the total intraluminal HPZ pressure. However, the true barrier to reflux is the intrinsic "tone" maintained by the esophageal muscle in this zone, which is not the same pressure as recorded by an intraluminal sensor.

In the Surgical Research Laboratory, in the Medical Sciences Building at the University of Toronto we carried out two interrelated studies that were designed to show that it was possible to measure the intrinsic tone of the HPZ as an entity, separating it from the pressure effects of the surrounding body cavities.

Method

Esophageal pressures were recorded using three polyethylene No. 190 tubes with side openings 5 cm. apart during constant infusion of water at 3.6 c.c./min./tube. The sensing devices were P23De Statham strain gauges and the recording device was a 1508 Honeywell visicorder.

The resistance of the tubes to forward flow of water was calculated by perfusing the tubes at the standard flow rate and recording the back pressure produced by this flow. This resistance was added to atmospheric pressure to calculate the baseline atmospheric pressure during the pressure recording.

The swallowed tubes were withdrawn from the stomach into the esophagus through the HPZ at 0.5-cm. intervals.

First Experiment

In this experiment (Part I), we studied the effect of elevating gastric pressure upon the respiratory positive and the respiratory negative HPZ. This study was carried out on 17 normal subjects and 14 patients with hiatus hernia. The subjects had been fasted for 12 hours before the study. The motility tubes were placed in the stomach and withdrawn through the HPZ as previously described. Manual abdominal compression was applied at each stage during withdrawal, and simultaneous measurements were made of gastric and HPZ pressures. We took measurements only in that portion of the zone which showed relaxation during deglutition. Abdominal compression was applied only when gastric and HPZ pressures were stable, i.e. were not being affected by pressure changes during swallowing.

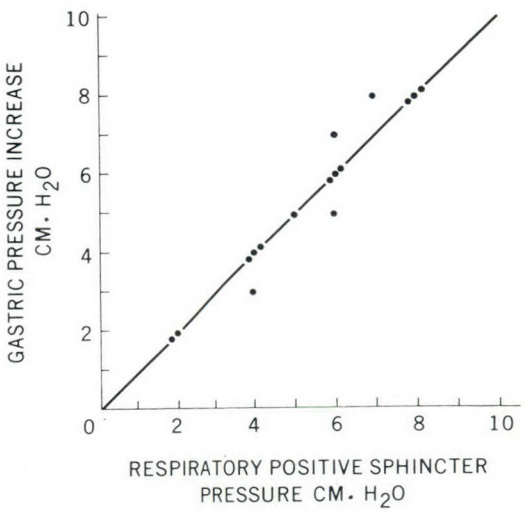

Fig. 3.—Comparison between the pressure increases in the stomach and in the respiratory positive sphincteric zone in normal subjects. The pressure increases were measured simultaneously during manual abdominal compression. The gastric pressure increase equalled the increase in pressure in the respiratory positive zone (± 1 cm. H_2O) of the gastroesophageal junction.

Results

In the respiratory positive HPZ in the 17 normal subjects, elevations of gastric pressure were associated with equal elevations of pressure in the HPZ ± 1 cm. H_2O (Fig. 3). In the 14 patients with hiatus hernias, the results were the same—equal elevations of pressure in the stomach and in the respiratory positive HPZ (Fig. 4).

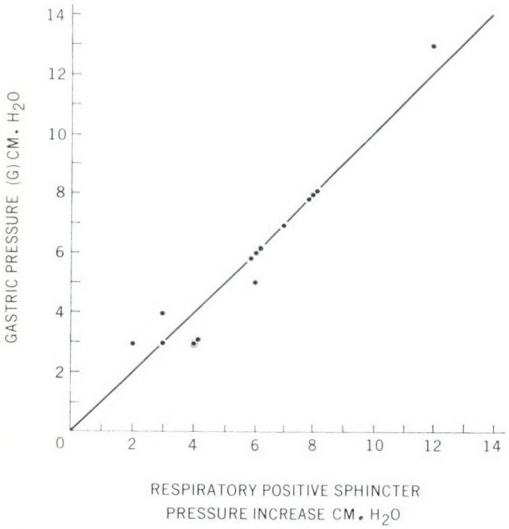

Fig. 4.—Comparison between the pressure increases in the stomach and in the respiratory positive HPZ during manual abdominal compression in patients with hiatus hernias. The increments of pressure increase (± 1 cm. H_2O) were equal in the stomach and in the respiratory positive zone of the gastroesophageal junction.

The respiratory negative HPZ responded in a different way. The pressure in the zone responded to increased gastric pressure in only six out of 17 normal subjects and five out of 14 patients with hiatus hernias. When the pressure in the respiratory negative HPZ did respond, the response was the same in the normal subjects and in the patients with hiatus hernias. The respiratory negative HPZ became respiratory positive and the pressure in the zone rose to equal the anticipated pressure rise in the respiratory positive zone (Fig. 5, Table I).

We could not record simultaneously the respiratory positive HPZ, the respiratory negative HPZ and the gastric pressure, so that in these studies we used respiratory positive HPZ pressures previously obtained

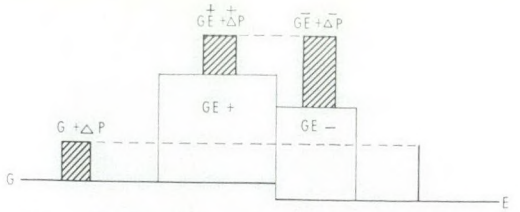

Fig. 5.—Response of the gastroesophageal sphincter to abdominal compression. When abdominal compression is applied manually, the pressure increase in the stomach equals the pressure increase in the respiratory positive gastroesophageal HPZ. The respiratory negative zone of the gastroesophageal junction may not respond to abdominal compression, but if there is a response, the respiratory negative zone becomes respiratory positive and the intraluminal pressure rises to equilibrate with the pressure in the respiratory positive HPZ. G = gastric pressure; ΔP = the increase in gastric pressure; G+E = the respiratory positive HPZ pressure and G-E the respiratory negative HPZ pressure; Δ+P and Δ-P = the pressure increases in the respiratory positive and in the respiratory negative zones, produced by abdominal compression; E = esophageal pressure.

to calculate the increase in pressure with abdominal compression in the respiratory negative HPZ. The correlation between gastric and respiratory negative HPZ pressure elevations was not as close as the correlation between gastric pressure and pressure elevations in the respiratory positive HPZ. This poor correlation probably reflects our inability to record gastric,

TABLE I.—Response of Respiratory Negative Sphincter to Abdominal Compression*

Patient	*PG*	$G\overset{+}{E} + \triangle\overset{+}{P}$	$G\overset{-}{E} + \triangle\overset{-}{P}$
Normal 2	8	30 + 8 = 38	18 + 18 = 36
Normal 4	2	16 + 2 = 18	12 + 5 = 17
Normal 8	5	18 + 5 = 23	14 + 8 = 22
Normal 9	–	20 + 2 = 22	12 + 7 = 19
Normal 10	8	16 + 8 = 24	12 + 10 = 22
Normal 17	6	16 + 6 = 22	20 + 1 = 21
Hiatus hernia 142	6	16 + 6 = 22	16 + 6 = 22
Hiatus hernia 149	8	10 + 8 = 18	14 + 4 = 18
Hiatus hernia 151	8	14 + 8 = 22	12 + 10 = 22
Hiatus hernia 191	3	14 + 3 = 17	8 + 6 = 14
Hiatus hernia 206	8	18 + 8 = 26	4 + 22 = 26

*When abdominal compression was applied, the respiratory negative zone responded by converting to respiratory positive, and the pressure rose to equal the pressure in the respiratory positive zone. This response was present in six out of 17 normal subjects and in five out of 14 patients with hiatus hernias. PG = the increase in gastric pressure with abdominal compression; G^+E and G^-E = the respiratory positive and respiratory negative HPZ pressures; $\triangle P^+$ and $\triangle P^-$ = the increase in pressure in the respiratory positive and respiratory negative zones.

respiratory positive and respiratory negative HPZ pressures simultaneously.

Second Experiment

Using the same technique as described in Part I, we studied 20 normal subjects and 50 patients with hiatus hernia to determine the degree of relaxation that occurred in the HPZ with swallowing (Part II). In this study, we included the subjects that we had already investigated to determine the response of the HPZ to abdominal compression.

Atkinson *et al.*,[5] in a study of the HPZ, defined the effective HPZ as the respiratory positive HPZ minus the gastric pressure and referred to this parameter as the "tone" of the HPZ. We have adopted this concept of HPZ tone in the experiment and have expressed relaxation with deglutition as a percentage of respiratory positive HPZ pressure minus gastric pressure in the distal HPZ, and as a percentage of respiratory negative HPZ pressure minus esophageal pressure in the proximal HPZ (Fig. 5).

Relaxation with swallowing was calculated using end-expiratory pressures. For each swallow the HPZ tone was calculated as the mean end-expiratory pressure in the HPZ immediately preceding relaxation minus (a) the mean gastric pressure in the respiratory positive HPZ, and (b) the mean lower esophageal pressure in the respiratory negative HPZ.

We recognized two types of relaxation in the respiratory positive zone (Fig. 6). In the more common type, the HPZ remained respiratory positive at the time of maximum relaxation. Here, relaxation, expressed as a percentage of calculated HPZ tone, was marked by a fall in end-expiratory pressure. In the second type, the respiratory positive pressure converted to respiratory negative during relaxation. Again, the fall in end-expiratory pressure was calculated and tone expressed as the difference between respiratory positive HPZ pressure and mean end-expiratory esophageal pressure.

In the respiratory negative zone, respiratory deflections during relaxation were always respiratory negative. Relaxation was expressed as a percentage of the difference between the respiratory negative HPZ pressure and the lower esophageal pressure.

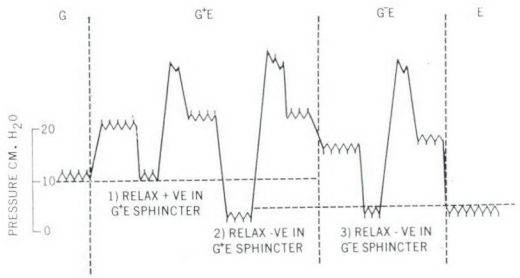

Fig. 6.—Relaxation in the gastroesophageal sphincter. There are two types of relaxation in the respiratory positive zone of the gastroesophageal junction. In the more common type, the pressure in the respiratory positive zone remains positive throughout relaxation. The fall in pressure is expressed as a percentage of tone, calculated by subtracting gastric pressure from the intraluminal pressure immediately before relaxation. If, during relaxation, the intraluminal pressure converts from respiratory positive to respiratory negative, the fall in pressure is expressed as a percentage of HPZ tone, calculated by subtracting mean esophageal pressure from the pressure in the respiratory positive zone immediately before relaxation.

TABLE II.—Gastroesophageal Sphincter Relaxation in Normal Subjects. Total of 106 Swallows Documented in 20 Normal Subjects*

Relaxation (%)	*Respiratory positive sphincter (91)*	*Respiratory negative sphincter (15)*
25 - 39	5	1
40 - 69	24	3
70 - 99	39	6
100	23	5

*In normal subjects, relaxation in the gastroesophageal junction was measured and expressed as a percentage of calculated HPZ tone. The maximum relaxation obtained was 100% of calculated tone. Although there was a wide variation in percentage relaxation, more than two-thirds of relaxations were greater than 70% of calculated tone, and 26.4% of relaxations were equal to 100% of calculated tone.

Results

In the 20 normal subjects, we analyzed 106 swallows using the method described. During 91 swallows we took measurements in the respiratory positive HPZ, and during 15 in the respiratory negative HPZ (Table II).

Twenty-eight of the 106 swallows induced 100% relaxation of calculated HPZ tone. No swallow induced relaxation greater than 100% of calculated HPZ tone. This 100%

relaxation of HPZ tone is of theoretical interest and will be discussed later.

The range of relaxation was wide, but most swallows produced relaxation greater than 70% of tone (Table II). In the respiratory positive HPZ, the average relaxation was 85% of tone in the respiratory negative HPZ.

In the 50 patients with hiatus hernias, HPZ relaxation was calculated in 115 swallows, 55 in the respiratory positive zone and 60 in the respiratory negative zone (Table III). Eleven swallows produced 100% relaxation of HPZ tone. Again, variation in the percentage of relaxation was wide, but the average relaxation was 63% in the respiratory positive HPZ, and 48% in the respiratory negative zone (Table III).

TABLE III.—Gastroesophageal Sphincter Relaxation in Hiatus Hernia Patients. Total of 115 Swallows Documented in 50 Patients with Hiatus Hernia*

Relaxation (%)	*Respiratory positive sphincter (55)*	*Respiratory negative sphincter (60)*
0 - 24	4	14
25 - 30	2	7
40 - 69	26	23
70 - 99	17	11
100	6	5

*In patients with hiatus hernias, relaxation in the gastroesophageal junction was measured and expressed as a percentage of calculated HPZ tone. The maximum relaxation obtained was 100% of calculated tone. Again, there was a wide variation in percentage relaxation but, in this case, two-thirds of the relaxations were less than 70% of calculated tone. Relaxations of 100% of tone occurred in 10% of deglutition. These results support previously published data and show reduced relaxation in association with hiatus hernias.

Discussion

Opinions differ concerning the response of the gastroesophageal HPZ to abdominal compression and several studies have produced different results. Lind, Warrian and Wankling[6] showed that the intraluminal pressure in the HPZ increased during abdominal compression. In this study, the measurements were not made simultaneously. Gastric and HPZ pressures were measured with the subject at rest, and the results of abdominal compression were recorded later. These circumstances, i.e. gastric and HPZ pressures were not simultaneously recorded, make comparison with the present study difficult.

Cohen and Harris[7] and Diamant and Harris[8] used an entirely different method to calculate HPZ response to abdominal compression. A Teflon ball was drawn through the HPZ and the resistance to the passage of the ball was calculated. In their studies, resistance to the passage of the ball increased when abdominal compression was applied. This technique is interesting but so radically different from the present study that again we can make no comparison.

Nagler and Spiro[9] demonstrated that there was a 1:1 pressure response between gastric and HPZ pressure when abdominal pressure was applied. The technique they used was similar to that in the present study, but they used an uninfused water-filled system; this again makes comparison difficult because the uninfused water-filled tube does not record pressure accurately and, in fact, records only relative pressure changes.

The first part of the current study compared directly pressure elevations in two zones induced by abdominal compression. The respiratory positive HPZ responded to abdominal compression by an equal elevation of gastric and HPZ pressures. In the respiratory negative HPZ, the comparisons were not direct and, hence, were less accurate. From the results obtained, it appears that the response of the respiratory negative zone was due to a proximal shift of the pressure reversal point (PRR) after which the pressure response equalled that in the respiratory positive HPZ.

In the first study, the respiratory positive HPZ responded to manual abdominal compression by a pressure rise which equalled the elevation of gastric pressure. When abdominal compression ceased, both gastric and HPZ pressures fell to the resting level. Theoretically, one can argue from this that, if gastric pressure were reduced to 0 cm. H_2O, there would be an equal pressure fall in the respiratory positive HPZ. We therefore theorized that, if all extrinsic pressure were removed from the gastric wall and the stomach was empty, we could reduce gastric pressure to 0 cm. H_2O. Under these

theoretical circumstances, respiratory positive HPZ pressure should fall by an equal amount. The remaining respiratory positive HPZ pressure would then reflect the "tone" of the HPZ esophageal muscle, unaffected by gastric or peritoneal pressure (Fig. 7).

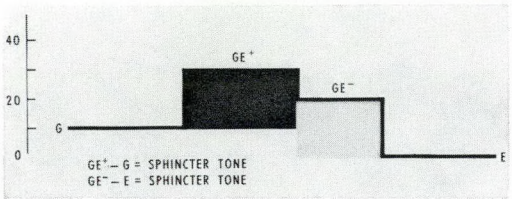

Fig. 7.—A theoretical calculation of gastroesophageal HPZ tone based upon the response of the gastroesophageal junction to increases in abdominal pressure and to the relaxation associated with deglutition. HPZ tone calculated in this way is equal to the respiratory positive pressure minus the gastric pressure, or the respiratory negative pressure minus the esophageal pressure. Sphincter tone is approximately equal in the respiratory positive and respiratory negative zones. The mean tone is the average of calculated respiratory positive and respiratory negative tone. G = gastric pressure; GE+ = the respiratory positive HPZ pressure; GE- = the respiratory negative HPZ pressure; E = the esophageal pressure.

We then studied this concept of tone at the gastroesophageal junction by examining relaxation with swallowing in the HPZ. Total relaxation in the HPZ would reduce the intrinsic tone to 0 cm. H_2O, but could not reduce the tone any further.

In Part I of the study, calculation of the HPZ tone was theoretical and based upon the response of the HPZ to abdominal compression. In Part II we proposed that if relaxation could reduce calculated HPZ tone to 0 cm. H_2O but no further, the response of the zone to relaxation would support this concept of tone by showing that the "tone" component of measured HPZ pressures was the only component capable of relaxing in response to a swallow.

In studying relaxation, we noted that in the normal subjects the relaxations in 28 of 106 swallows equalled 100% of calculated tone and, in the hiatus hernia patients, 11 of 115 swallows produced 100% relaxation.[10-12] In no instance did a swallow produce relaxation greater than 100% of calculated tone. This, we concluded, suggested that tone was a measurable entity in the HPZ because relaxation only affected that component of the HPZ pressure which had been calculated as HPZ tone.

One other interesting facet of this study deserves consideration. As noted earlier, the PRR in hiatus hernia patients may lie above the anatomical diaphragm and, for this reason, the location of the PRR cannot depend solely upon its position within the thoracic or abdominal cavities. This being the case, the PRR must be an expression of some other system of pressure transmissions; the most obvious is the intraluminal transmission of pressure from the stomach or the esophagus. When abdominal compression was applied in this study, the PRR in 11 subjects shifted proximally and the respiratory deflections converted from respiratory negative to respiratory positive. This proximal shift in the PRR was found in both the normal subjects and the patients with hiatus hernia. It is unlikely that in response to abdominal compression the gastroesophageal HPZ would actually descend and indeed, radiologically, the junction usually can be shown to ascend with abdominal compression. Therefore, the respiratory positive HPZ probably moves proximally because the respiratory positive pressures are in part transmitted intraluminally, and with abdominal compression such transmission shifts the PRR proximally in the HPZ.

Summary

In Part I we studied the response of the gastroesophageal HPZ to abdominal compression in 17 normal subjects and 14 patients with hiatus hernia. The pressure increase in the respiratory positive HPZ was equal to the gastric pressure increase. In the respiratory negative HPZ when the pressure increased it was associated with a proximal shift of the respiratory positive HPZ; the pressure then rose to equal the respiratory positive HPZ pressure.

A theoretical calculation of HPZ tone was made from these observations and the tone of the HPZ was defined as: (a) the respiratory positive HPZ minus gastric pressure, or (b) the respiratory negative HPZ minus esophageal pressure.

In Part II, a study of relaxation in response to swallowing, we found that 39 of 221 swallows gave relaxation equal to 100% of calculated HPZ tone. None of the relaxations was greater than the calculated HPZ tone. This, we conclude, adds support to the concept of tone as a measurable entity, because relaxation only occurred in that component of the HPZ pressure which had been calculated as HPZ tone.

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Résumé

Dans la première partie de la présente étude, les auteurs ont étudié, sur 17 sujets normaux et 14 malades souffrant de hernie hiatale, la réaction de la zone à haute pression (ZHP) de la région gastro-oesophagienne à la compression abdominale. L'augmentation de pression dans la ZHP sous pression respiratoire positive était égale à l'augmentation de la pression gastrique. Dans la ZHP sous pression respiratoire négative, quand la pression augmentait, elle était accompagnée de déplacement proximal de la ZHP sous pression respiratoire positive: la pression a monté ensuite et était alors égale aux pressions de la ZHP sous pression respiratoire positive.

De ces observations, les auteurs ont tiré un calcul théorique de la tonicité de ZHP, qu'ils définissaient comme suit: (a) la ZHP sous pression respiratoire positive, moins la pression gastrique, (b) la ZHP sous pression respiratoire négative, moins la pression oesophagienne.

Dans la seconde partie, consacrée au relâchement déclenché par la déglutition, les auteurs ont trouvé que sur 221 actes de déglutition, 39 ont amené un relâchement du tonus égal à 100% du tonus calculé de la ZHP. Dans aucun cas, ce relâchement n'était supérieur au tonus calculé de la ZHP. D'après eux, cette constatation vient confirmer le principe du tonus, considéré comme une entité mesurable. En effet, le relâchement ne s'est produit que dans la composante de la pression de la ZHP qui avait été calculée comme exprimant le tonus de la ZHP.

POST-TRAUMATIC CARDIOCORONARY FISTULA

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COMMUNICATIONS between the coronary vessels and the cardiac chambers are infrequent and are usually congenital.[1] They present as a continuous murmur similar to a patent ductus arteriosus, but the point of maximal intensity is usually at the lower left sternal edge. The commonest communication is between the right coronary artery and the right ventricle.

Cardiocoronary communication after blunt trauma to the chest wall, however, is exceedingly rare. For this reason we present a 21-year-old man who was admitted with frank congestive heart failure, after blunt trauma to the chest in an automobile accident had opened a communication between the right coronary artery and the right ventricle.

CASE REPORT

R.G., a 21-year-old man, was in excellent health except for occasional asthma until February 1965 when he sustained a severe injury to the anterior chest in a car accident. He was unconscious for several days and was said to have had a bilateral hemothorax. After the accident he became progressively short of breath on exertion and had occasional precordial pain. Also, he had two episodes of syncope in the two months before admission and, when admitted, could walk only a few blocks without shortness of breath.

When admitted to the Kingston General Hospital for investigation on September 22, 1965, he was well nourished and had no distress at rest. His blood pressure was 130/80 mm. Hg; temperature was normal; pulse was 68/min. and regular; respiration was 20/min. The apex beat was in the axillary line at the sixth interspace. A Grade 3 "machinery" murmur was audible at the left sternal edge in the second to fourth interspaces. The liver was palpable 3 cm. below the costal margin.

A radiograph of the chest showed cardiomegaly and the electrocardiogram showed right-axis deviation with right ventricular hypertrophy. Cardiac catheterization confirmed a shunt in the outflow tract of the right ventricle, *viz.* increased oxygen saturation in the outflow tract and normal pressures. Cineangiography showed a fistulous communication between the right coronary sinus of Valsalva and the right ventricle, with no filling of the right coronary artery.

Before the accident this patient had no history of cardiovascular abnormalities; his previous records were reviewed, including an admission to the Vancouver General Hospital in May 1964, eight months before.

At open-heart operation for correction of an aorticoventricular fistula, the right ventricle was opened using cardiopulmonary bypass and a linear opening was found which, on probing, communicated with the root of the aorta. This examination suggested that a fistula existed between the outflow tract of the right ventricle and the related sinus of Valsalva. The communication was closed with a Teflon patch which was applied to the opening into the outflow tract of the right ventricle. The patient was discharged from hospital on the thirteenth postoperative day at which time he had a soft Grade 2 diastolic murmur detectable in the second to fourth interspaces precordially. His convalescence was uneventful until about six weeks after operation when, while swinging his young brother around at play, he felt a tearing sensation in his chest. A feeling of weakness soon overcame him and he became progressively short of breath. On follow-up examination the murmur had returned in the original location. Catheterization again demonstrated a shunt at the ventricular level, and cineangiography showed shunting between the root of the aorta and the right ventricle. At this time the coronary artery was visualized on the angiogram.

At a second operation in December 1965, the root of the aorta was opened with a view to closing the aortic end of the suspected sinus-of-Valsalva fistula. To our surprise we found no fistula and concluded that the communication was between the main right coronary artery and the right ventricle (Fig. 1). The right coronary artery was therefore ligated and oversewn. His postoperative course was uneventful. This patient returned to the Kingston General Hospital in April 1970 and, on cardiac catheterization and angiogram, the cardiac hemodynamics were normal.

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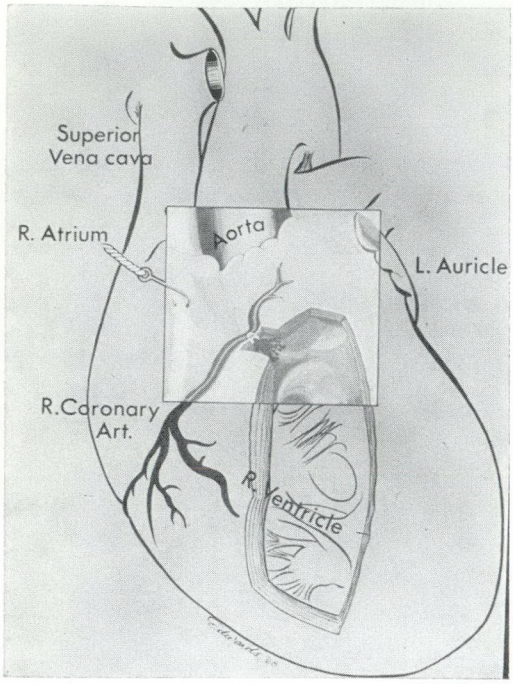

Fig. 1.—Artist's conception of what was found at the second operation in December 1965.

Discussion

In the most common type of cardiocoronary communication, a fistulous tract connects the right coronary artery to a low-pressure chamber, usually the right ventricle. These communications are invariably congenital and, to prevent heart failure and subacute bacterial endocarditis, they should be repaired electively.

Communications between the coronary vessels and the cardiac chambers, which are a complication of trauma, are exceedingly rare. In a recent report of 22 coronary lacerations[2] the overall mortality rate was 55% and none of the survivors had cardiocoronary fistulas.

In another series of 197 open cardiac injuries,[3, 4] three patients developed aortic-to-right-ventricular fistulas but no cardiocoronary communications.

The commonest electrocardiographic abnormality recorded after trauma to the anterior chest, such as a steering-wheel injury, is inferior-wall infarction. Such a finding implies injury to the right coronary artery—probably anteriorly. In our patient, a pericoronary hematoma probably developed around the torn or severely contused coronary artery, which later ruptured into the thin-walled infundibulum of the right ventricle, thus producing the fistulous communication. When such a complication of chest trauma is suspected, the surgeon must explore at once both the outflow tract of the right ventricle and the root of the aorta in order to preserve continuity of the coronary artery if possible. Our patient, however, has done well despite interruption of the right coronary flow.

Summary

A 21-year-old man developed cardiocoronary fistula after blunt injury to the chest. Such an injury is exceedingly uncommon and could be confused with rupture of the sinus of Valsalva in the right heart, as was suspected in our case. The correct diagnosis was made at the second operation and the defect repaired. The patient remains well five years after surgical correction of the communication.

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Résumé

Après un traumatisme externe sur le thorax, un homme de 21 ans présenta une fistule cardiocoronarienne. Cette lésion, extrêmement rare, peut être confondue avec la rupture du sinus de Valsalva dans le cœur droit, comme nous l'avions cru dans notre cas. Le diagnostic exact fut porté lors de la seconde opération qui permit de corriger la communication. Cinq ans après cette opération, le malade est bien portant.

REFRACTORY HYPOTENSION*

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A RAPID fall in blood volume (as in hemorrhage) or in cardiac output (as in acute heart failure) stimulates carotid sinus and aortic arch baroreceptors, which reflexly activate sympathetic nerve endings to release noradrenaline. Vessels constrict in the skin, kidneys and splanchnic beds, relatively preserving coronary and cerebral blood flows. In sepsis, bacterial endotoxins augment sympathetic vasoconstriction. Patients who remain in shock may develop, after a time, hypotension refractory to the commonly employed resuscitative measures. The term "irreversible shock" is derived from an experimental preparation in the animal laboratory,[1] but in humans has been applied to the state of progressive hypotension, which so far has resisted treatment.

Irreversible shock is produced experimentally by maintaining a preselected level of hypotension by withdrawing blood into a reservoir connected to a dog's femoral artery. After a time, the dogs show signs (such as the uptake of shed blood from the reservoir in order to prevent a decline in arterial pressure and bleeding from the gut) that indicate that a certain number will die, even though for a time the blood pressure will respond to reinfusion of all the withdrawn blood and some additional replacement.

Before hypotension in the human is designated "refractory", possibly overlooked causes of low blood pressure should be sought.[2] Table I gives some examples. The actual cause of persisting low blood pressure may be myocardial deficiency, inadequate replacement, or invasive infection. Hyponatremia or hyperkalemia may co-exist, possibly due to rare acute adrenal insufficiency. Hypocalcemia may develop after transfusion of 10 units of blood if hepatic anoxia has destroyed the liver's ability to metabolize citrate.[3] The patient may have an unrecognized gastrointestinal perforation. Because several causes may co-exist, each must be treated in turn. This paper will describe several theories which attempt to explain refractory hypotension in man.

TABLE I.—SOME CAUSES OF PERSISTING LOW BLOOD PRESSURE

(1)	Pre-existing myocardial damage
	Acute myocardial infarction
	Myocardial contusion
	Toxic myocardial damage
	Cardiac tamponade
	Pneumothorax or hemothorax
(2)	Inadequate replacement of fluid
	Unrecognized or continued bleeding
	Occult volume deficit (e.g. fulminant pancreatitis)
3)	An occult abscess

ENDOTOXEMIA

Fine's theory[4] is based mainly on his work in dogs in which transmural migration of intestinal bacteria into the portal circulation releases *endotoxin*, a lipopolysaccharide, from the cell walls of disintegrating bacteria. Endotoxin is normally destroyed by the reticuloendothelial system (RES). Fine postulated that, in refractory shock, whether due to gram-negative infection, severe and persisting hypovolemia, or acute myocardial infarction, the ischemia due to prolonged splanchnic vasoconstriction progressively damages the RES in the liver and spleen.[5-8] The refractory state, he believes, develops when a factor that normally detoxifies endotoxin is depleted in the RES and when the phagocytic defence of the RES fails. When these defences fail, endotoxin absorbed from the gut produces progressive deterioration of the peripheral circulation.

This theory proposes that, if it lasts long enough, septic shock is the final common pathway for ischemic shock.[9-11] Endotoxin intensifies the vasoconstriction and interacts with some component of cells, possibly lysosomal enzymes.[4, 12] The concept implies that patients with refractory hypotension should receive antibiotics in doses adjusted according to the adequacy of renal func-

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tion. Fine has been trying to isolate the active antiendotoxic principle, presumably an enzyme, from the reticuloendothelial cells. This, of course, would provide specific treatment for such hypotension.[4]

Disseminated Intravascular Coagulation

According to Hardaway, the refractory state is caused by disseminated intravascular coagulation (DIC).[13, 14] *Coagulation* and *lysis of thrombi* within the vessels is a normal dynamic process. Fibrin is formed and destroyed at the same rate by fibrinolysin (Fig. 1). In shock, whether hemorrhagic, burn, septic, or cardiogenic, this equilibrium shifts and red-cell aggregation and agglutination occur.[15] Platelet agglutination and red-cell disintegration liberate thromboplastin, leading to fibrin deposition.[16, 17] The resulting thrombosis obstructs the microcirculation in the lungs, liver, kidney, heart, spleen and other organs.[13]

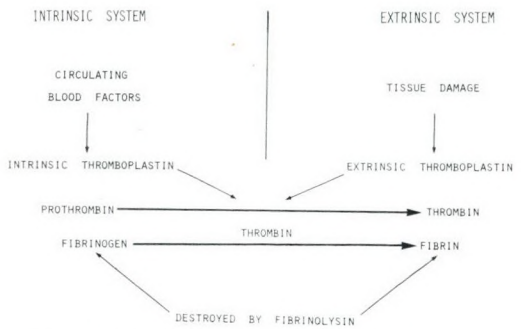

Fig. 1.—Simplified scheme of blood coagulation.

Hemorrhage, the production of endotoxin, or the decreased cardiac output secondary to myocardial deficiency liberates catecholamines into the circulation and produces arteriolar constriction.[18] Peripheral anoxia causes local mast cells to liberate histamine so that all capillaries (80% of which normally are closed at one time) open.[19, 20] With this great increase in the volume of the vascular tree, flow in the capillaries slows or stagnates, leading to an increase in lactic-acid production from anaerobic metabolism. The pH drop across the capillaries is marked. Slow-flowing (and thus viscous)[21] acid blood is hypercoagulable and, with the addition of thromboplastin from hemolyzed cells, produces DIC in late shock.[20]

In irreversible shock, although circulation may be restored by replacing blood volume and lysing microthrombi by endogenous fibrinolysin, cells nourished by the formerly occluded capillaries are now dead. If this is widespread, focal necrosis causes organ failure, for example, in kidney, liver or adrenal. The lung shows areas of hemorrhage, thrombi and atelectasis but not necrosis.[13]

Disseminated intravascular coagulation promotes secondary arteriolar spasm, producing a vicious circle. Moreover, platelet aggregates liberate serotonin, which causes arteriolar constriction,[22] and the conversion of fibrinogen to fibrin by thrombin splits off two peptides (cofibrin A and B) which cause vasoconstriction.[13]

In septic shock, endotoxin itself produces platelet stickiness and clumping. Furthermore, the RES, which normally removes fibrin fibres from the circulating blood and protects against DIC, may be inefficient. In crush injuries, tissue thromboplastin enters the blood stream.[23]

In burns, injury to the vessel wall leads to accumulation of platelets and the high hematocrit increases blood viscosity,[24] reducing cardiac output and reducing oxygen transport to the tissues.[25]

Hardaway's concept of DIC stresses the value of adequate proper volume replacement, and he recommends the use of vasodilators (corticosteroids, isoproterenol or phenoxybenzamine), and the correction of acidosis and thus of hypercoagulability.

Arteriolar Relaxation and Capillary Pooling

R. C. Lillehei and his group[26] have also suggested that refractory shock is caused by peripheral, congested, stagnant anoxia, but they offer a different explanation from Hardaway (Fig. 2). According to their concept, catecholamines constrict *both* precapillary arteriolar sphincters and postcapillary venular sphincters. With arteriolar constriction, the hydrostatic pressure transmitted from the arteries to the capillaries is decreased and tissue fluid filters

into the vascular bed. As the shock state continues, the increasing acidosis makes the arterioles less responsive to catecholamines. The arterioles and precapillary sphincters lose their tone, but venular sphincters maintain their tone[26-29]—possibly because the venular side normally functions at a lower pH than the arterial side. As a result, blood is trapped in stagnant peripheral pools. The hydrostatic pressure is now greater than the colloid osmotic pressure in the capillaries, and fluid is forced out into the tissues. As stagnant anoxia continues, the capillary walls lose their integrity, and an *irreversible* state develops. Blood and volume expanders are retained only temporarily in the circulation.

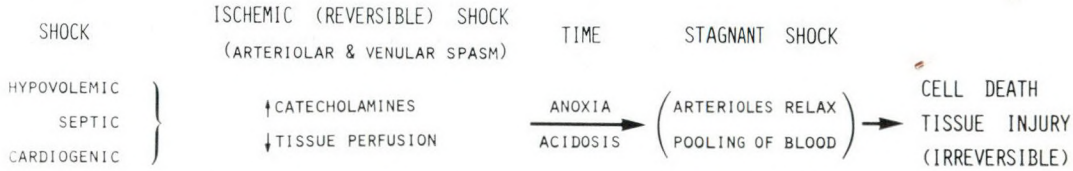

Fig. 2.—Progress of shock to irreversibility (after R. C. Lillehei[26]).

Treatment implies prevention before the shock state becomes entrenched. Isoproterenol, glucocorticoids or phenoxybenzamine is used to relieve shock unresponsive to volume replacement. Lillehei's group uses massive doses of glucocorticoids to achieve pharmacologic action (Table II).

TABLE II.—Actions of Massive Doses of Glucocorticosteroids

(1) Reduce peripheral resistance. Restore the normal relationship between arteriolar and venular sphincter tone[26, 62-64]
(2) Increase myocardial contractility[62-64]
(3) Stabilize membranes of cells and of intracellular lysosomes, preventing release of lytic enzymes and digestion of the cells[59, 64, 65]
(4) Promote conversion of lactate back to glucose[50, 66, 67]
(5) Decrease hypersensitivity to endotoxin[65]

In the dog, the ischemic phase produces hemorrhage into the gut. As the stagnant phase develops, the mucosa of the intestine becomes necrotic. Congestion and stagnant anoxia are also present in the kidney, liver and lungs, but are most marked in the intestine.[26] The target organ differs in different animals. In the dog,[2, 30-32] the gut is most sensitive to the effects of anoxia; in the cat and in the human it is the lung.

Endotoxin shock follows the same course as hemorrhagic shock: endotoxin causes intense vasoconstriction of arterioles and venules, the former eventually relaxing. Acute myocardial failure also follows the same common pathway to irreversibility.[26]

Pulmonary Changes: Congestive Atelectasis

Patients in refractory shock may die of pulmonary failure due to congestive atelectasis.[19, 33-35] Histologically, there is collapse (without obstruction) of the pulmonary alveoli with intense interstitial pulmonary capillary congestion, hemorrhages, and fibrin deposition, often in a patchy distribution (Fig. 3). Early in shock the chest radiograph shows little change, but later there is patchy or diffuse opacification in the lung fields (Fig. 4).

Congestive atelectasis inhibits the osmotic exchange of gases between the alveoli and the capillaries. In this state the lungs are stiff and compliance is decreased. Respiratory work is increased (further increasing metabolic needs), unless artificial ventilation is used.[35, 36]

A number of factors may cause these pulmonary changes.

(1) Arteriovenous shunting of blood through the lungs decreases perfusion of the pulmonary capillary bed[37] and causes hypoxia of pulmonary tissue.

(2) Surfactant, a phospholipoprotein synthesized in the mitochondria of alveolar type II epithelial cells, lines the alveolar surface. Surfactant has a low surface tension and keeps the alveoli open on expiration. With hypoxia and the resulting depression of metabolic activity in the lung, previously synthesized surfactant is de-

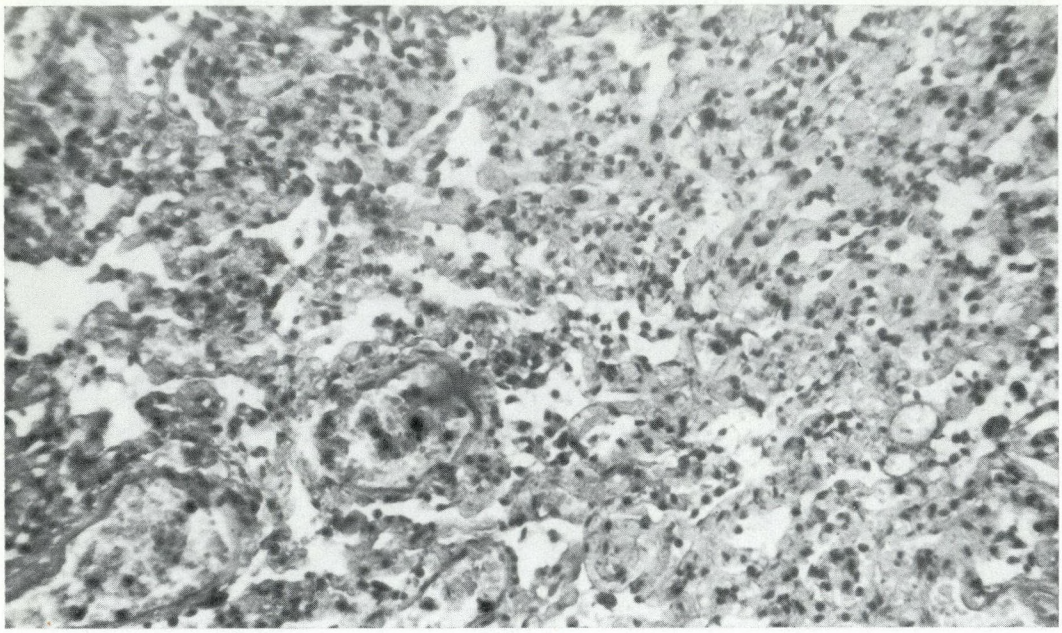

Fig. 3a

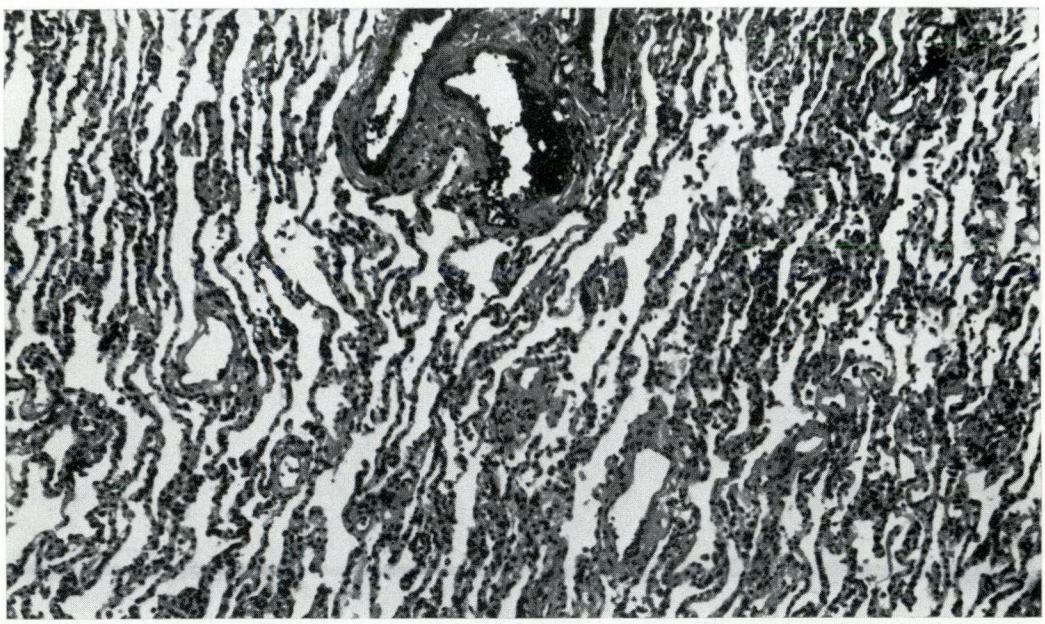

Fig. 3b

Fig. 3.—(a) Photomicrograph of a section of the lung from a patient who died after prolonged hemorrhagic shock from a massive retroperitoneal hematoma. Note the congestion of capillaries. Under high power, the individual red blood cells could not be distinguished. Sludging has occurred. Hemorrhages are present in the alveolar septa. The alveoli show collapse. These changes had a spotty distribution: in some areas the collapse was less marked than this, in others more. Marked collapse was present in sites in the right middle lobe and in the lower lobes, with dense liver-like areas of hemorrhage and atelectasis. These lungs are highly susceptible to bacterial invasion (× 50). (b) For comparison, a photomicrograph of pure obstructive atelectasis from a patient *not* in prolonged shock. Note that the alveoli are collapsed, but there is no interstitial vascular engorgement (× 50).

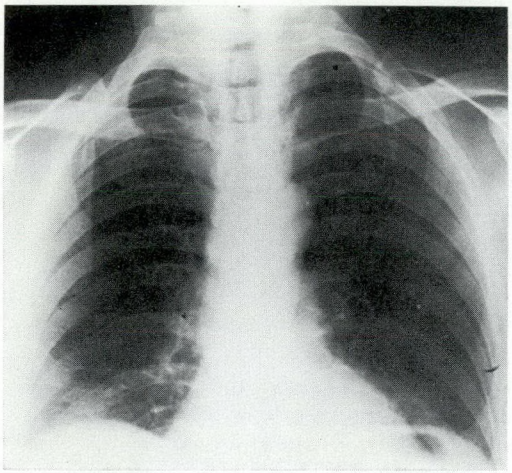

Fig. 4a

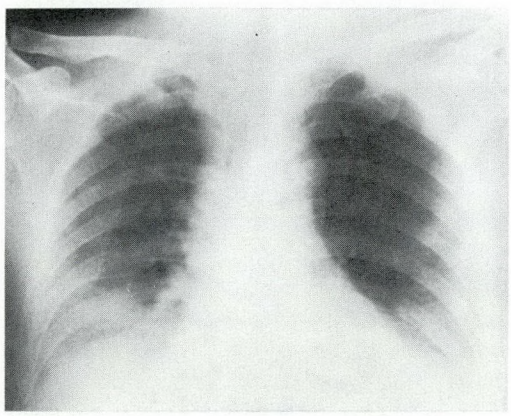

Fig. 4b

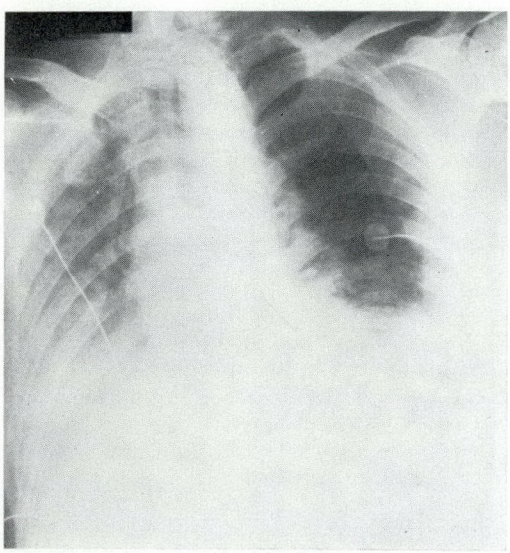

Fig. 4c

pleted but not replaced. Hence, alveolar surface tension increases and many alveoli collapse.[38-40]

(3) With hypoxia and acidosis in the lungs, the pulmonary capillaries dilate, blood flow slows, and congestion produces intravascular coagulation, especially if the hematocrit and blood viscosity are high. Sludging in the pulmonary capillaries causes pulmonary engorgement and alveolar collapse.[13, 17, 19, 35] Shires[41-44] believes that, in shock, extracellular fluid moves into the cells, and the increasing concentration of intravascular colloid markedly impedes flow in small vessels if extracellular fluid replacement has not been adequate.

(4) Serotonin released from disintegrating platelets causes pulmonary vasoconstriction.[22, 35] Tissue breakdown liberates vasoactive kinins.[35, 39, 45]

(5) Circulatory overload with large volumes of crystalloid solution and blood causes pulmonary congestion and "wet lung".[46]

(6) If respirator therapy is being given, too high an oxygen concentration administered in the gas mixture produces edema and congestion of alveolar septas, pulmonary hemorrhage, atelectasis, and hyaline membranes lining the alveoli.[47]

(7) Inadequate humidity in the administered respirator air-mix may cause pulmonary changes.

Generally in shock, if the oxygen tension is below normal, oxygen should be administered by nasal catheter or respirator, and the oxygen concentration kept as low as possible to maintain a Po_2 of 70 to 80 mm. Hg.[19]

To treat congestive atelectasis, McClelland[48, 49] administers 100% oxygen by positive pressure respirator at high pressures and high flow rates, and curtails intravenous fluids. To prevent such atelectasis he replaces extracellular fluid without excessive blood.

Fig. 4.—Radiographs showing the progression in the patient who died after prolonged uncontrollable hemorrhage (Fig. 3a). (a) After a period in shock, fine areas of interstitial thickening are seen in the lower lung fields. (b and c, patient supine) Note the progression. In (c), there is extensive patchy distribution; the basal haziness is due to atelectasis and *not* effusion (note that the ribs are closer together in c than in b).

Significant Irreversible Cellular Damage

Ultimately, cellular changes determine the irreversibility of shock. Within the cell, cytoplasmic organelles (mitochondria) produce adenosine triphosphate (ATP) from breakdown of sugars, fats and amino acids. ATP has a high-energy phosphate bond which is the source of energy for cellular metabolism. In anaerobic metabolism, less ATP is produced.[50-52]

Fuelled by ATP, cell-membrane pumps normally hold potassium ions within the cell and keep sodium ions outside the cell, but when ATP is no longer available the cell membrane cannot maintain this differential across the cell wall. Then sodium and water enter, and potassium leaves the cell.[42, 50, 53, 54]

These concepts are confirmed, in part at least, by the following evidence: when red cell sodium and potassium content are measured in humans in profound shock, intracellular sodium is elevated and intracellular potassium decreased.[55] Also in human shock, measurements of potential difference across the cell membrane of skeletal-muscle cells, using a percutaneous electrode, show a loss of the ionic differential; when treatment restores adequate oxygen delivery and perfusion, the membrane potential returns to normal.[55, 56] Furthermore, in shock, when interstitial fluid is withdrawn via a micropipette in fascial planes between muscles in the rat's and dog's thigh, potassium is increased and interstitial fluid and sodium are decreased.[56, 57] Also, electron-microscope studies show intracellular edema in striated muscles, renal tubules and liver cells, with mitochondrial swelling and rupture.[58]

Lack of ATP means lack of energy for protein synthesis, and therefore decreased ability to combat shock, especially bacteremic shock, where antibody production is important.

Another important cause of irreversibility involves the lysosomes, which are cytoplasmic sacs of enzymes essential for normal intracellular digestion. With intracellular metabolic acidosis, however, the lysosomal membrane ruptures and releases these enzymes, which digest the cell, enter plasma and digest tissues.[50, 59, 60]

Hence, if deficient perfusion and oxygenation are not treated, shock ultimately becomes refractory when cells are damaged beyond repair.

Comment

There is overlap in the concepts proposed to explain the refractory stage that develops after prolonged and/or deep shock. One theory does not exclude the other, and all theories may be operative in varying significant degrees, depending on the etiology and development of the shock in the patient. New theories will appear. Recently, Wright[61] suggested that in septic shock, bacterial toxins act primarily on the cells (and not on the blood vessels) by affecting the mitochondria so that aerobic metabolism cannot occur. Thus, although oxygen does reach the cells, oxygen consumption falls, accounting for a low arteriovenous oxygen difference. Wright places prime importance on antibiotics in the treatment of septicemic shock.

In all the other theories, the deleterious effects of excessive constriction of peripheral blood vessels by sympathetic nerves seem to be basic. Administration of appropriate fluids and use of drugs producing vasodilation or blockade of the excessive sympathetic - nervous - system overactivity provide the best treatment at the moment.

Summary

The theories advanced to explain refractory shock may be summarized as follows:

All forms of shock, if they continue long enough, become endotoxin shock, because ischemia impairs the ability of the RES to detoxify endotoxin absorbed from the gut.

Anoxia due to vasoconstriction causes histamine release, dilated capillaries and stagnant acid blood. Clumping and disintegration of red cells and platelets, release of thromboplastin, and coagulation lead to death of cells nourished by the capillaries.

Initially, there is arteriolar and venular spasm. With prolonged shock, arterioles relax but venules remain constricted, resulting in peripheral pooling, stagnant anoxia and tissue death.

Changes in the lungs (congestive atelectasis) lead to inexorable pulmonary insufficiency.

Ultimately, if prolonged deficient perfusion and oxygenation continue, shock becomes refractory when there is significant irreversible cellular damage.

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RÉSUMÉ

Chez les malades en état de choc, une hypotension résistante aux moyens classiques de réanimation risque de survenir. Pour expliquer ce choc rebelle, diverses théories ont été proposées:

(1) Toutes les formes de choc finissent par devenir un choc toxi-infectieux parce que l'ischémie entrave la capacité du système réticuloendothélial de détoxiquer l'organisme des endotoxines absorbées au niveau du grêle (Fine).

(2) L'anoxie périphérique par vaso-constriction déclenche la libération d'histamine, la dilatation des capillaires et la stagnation d'un sang acide. L'agglomération et la désintégration des érythrocytes et des plaquettes, la libération de thromboplastine, la coagulation intravasculaire provoquent la mort des cellules qui sont irriguées par les capillaires (Hardaway).

(3) Au début du choc, artérioles et veinules entrent en spasme. A mesure que le choc progresse, on observe simultanément le relâchement des artérioles et la persistance de la constriction des veinules, d'où accumulation de sang périphérique, anoxie de stase et mort cellulaire (R. C. Lillehei).

(4) Des modifications pulmonaires (atélectasie congestive) mènent inexorablement à l'insuffisance pulmonaire.

(5) Longtemps soumise à une perfusion et à une oxygénation insuffisantes, la membrane cellulaire ne parvient plus à maintenir l'équilibre ionique. La rupture des lysosomes libère des enzymes autolytiques. Le choc devient rebelle et s'accompagne de lésions cellulaires irréversibles.

Toutes ces théories ont des facteurs communs et peuvent être invoquées à des degrés divers. On a émis récemment l'hypothèse que, dans le choc toxi-infectieux, les toxines affectent principalement les cellules (et non pas les vaisseaux) et créent un bloc métabolique dans les mitochondries.

ANEMIA FOLLOWING THERMAL BURNS: A SURVEY OF 109 CHILDREN

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ANEMIA in burns, its many causes and its management, has not been sufficiently discussed in the literature. This paper examines current concepts in burn anemia and describes briefly the authors' experience in its management. No attempt is made to review the literature in detail. This paper also describes a survey of the management of anemia in 109 thermal-burn patients treated at the Hospital for Sick Children, Toronto, between the years 1952 and 1968.

The administration of intravenous fluids to seriously burned patients has been recognized as a major part of their treatment for many years, and several formulas have been proposed to determine the quantity of fluid necessary for individual patients.[1] Because fluid replacement, colloidal and non-colloidal, is more urgent than erythrocyte replacement, the mechanisms of loss and methods of replacing extracellular fluid have been more strongly emphasized than erythrocyte loss and replacement. Because of this, the quantity of blood included in the various fluid formulas varies widely.[2]

During the "shock phase" of thermal burns, the physician must, of course, prevent oligemia and hypoxemia, but during all phases of such injury he must prevent or treat anemia because, during the septic and healing phases, anemia impairs the general metabolic response and the body's ability to resist infection, and inhibits healing.

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PATHOPHYSIOLOGY OF THERMAL-BURN ANEMIA

Major thermal burns are always accompanied by significant erythrocyte destruction and loss. The patient may require a blood transfusion at any time—from shortly after the injury until the wound is healed. In discussing the causes of anemia in thermal burns, we have arbitrarily chosen three periods: early, delayed and late (Table I). Almost at once, burning reduces red blood cell volume by trapping erythrocytes in the burned tissue, and a few hours after the burn delayed erythrocyte loss begins. Later, usually after the second week, infection and operation make the major contribution to anemia.

TABLE I.—ETIOLOGIC FACTORS IN ANEMIA FOLLOWING THERMAL BURNS

Early
1. Erythrocyte destruction and trapping
2. Intravascular sludging, venous pooling
3. Hemorrhage: local, general

Delayed
1. Continuing destruction of altered erythrocytes
2. Hemorrhage from the wound
3. Gastrointestinal hemorrhage
4. Depressed erythropoiesis

Late
1. Infection—
   (a) Increase of local hemorrhage
   (b) Depression of erythropoiesis
   (c) Hemolysis
2. Operation—
   (a) Hemorrhage with dressing changes
   (b) Hemorrhage with excision and grafting

EARLY CAUSES OF ANEMIA

Immediate erythrocyte destruction and the losses occurring in the first few hours can be considered together because the physician usually makes his assessment and starts treatment several hours after the burn. Temperatures high enough to pro-

duce charring and coagulative necrosis of skin and subcutaneous tissues produce thrombosis, and immediately destroy or trap erythrocytes in the damaged tissue. In adjacent tissue where the thermal injury has been less severe, other erythrocytes will be destroyed or injured.

Kimber and Lander[3] found that erythrocytes are lysed, fragmented, and agglutinated at 50° C. and above. These agglutinated erythrocyte masses are removed by the liver. Less severely injured erythrocytes, which are osmotically and mechanically fragile, are removed by the spleen or liver. Those only mildly damaged become spherocytes and are also removed by the spleen.

Intravascular hemolysis produces hemoglobinemia and hemoglobinuria. The microscopic hematuria frequently found in these patients may reflect the "functional hematuria" secondary to renal vasoconstriction, hypoxia and increased capillary permeability,[4] or it may be due to the trauma of bladder catheterization. Stasis in the microcirculation, both in the burned area and at some distance, removes erythrocytes from the effective circulation, as in extensive trauma or shock due to other causes.[5]

Studying the increased tendency of blood to clot after thermal injury in mice, Holder, Malin and Fox[6] found that hypercoagulability appeared minutes after the burn, reached a peak at three to five hours, and lasted about 24 hours. This hypercoagulability was not the result of hemoconcentration and was not solely responsible for the serious effects of the burn because heparinization did not improve survival rates. They produced a similar type of hypercoagulability in experimental animals by injecting an extract containing thromboplastin obtained from burned or unburned skin.

Theoretically, thermal burns should induce fibrinolytic states or consumption coagulopathies but, at the Hospital for Sick Children, Toronto, we have never recognized this complication. Without associated mechanical trauma, hemorrhage rarely causes early anemia in patients with thermal burns.

Delayed Causes of Anemia

Recent investigations of anemia in thermal burns[7-9] have been concerned mainly with the causes and extent of delayed erythrocyte loss. The loss of erythrocytes due to heat hemolysis is most dramatic in the 12 to 48 hours after the burn but it may continue for several days. Red blood cell loss due to hemolysis is related neither to the extent nor the depth of the burn.[9]

Davies and Topley[7] described a further delayed loss of the patient's own erythrocytes as well as transfused erythrocytes, which suggests that some as-yet-unidentified factors reduce the life-span of these cells.

Hemorrhage from the burned surface is not a common cause of anemia during this phase, but minor trauma to open burned surfaces (rubbing against sheets and bed sides or scratching) leads to repeated small blood losses. If the burn is complicated by infection and maceration, hemorrhage is more common.

Acute ulceration of the upper gastrointestinal tract, Curling's ulcer,[10] may cause blood loss in the first few days or weeks. Such bleeding developed from several hours to 111 days after burns ranging in extent from 1% to 95% of the body surface area.[11] Bleeding may be slight and chronic, or massive and acute. Ousterhout and Feller[12] found that 58% of their patients with thermal burns had significant amounts of occult blood in the stool.

Late Causes of Anemia

Two weeks after burning the most significant blood loss is that associated with repeated dressing changes; removal of the dressings in the burn bath reduces this. Brisk bleeding can occur from a burn area during eschar removal or from a graft donor area. When measured, the amount of blood loss is often greater than it appears.

Other causes of hemorrhage are occasionally important. Wound infection increases the tendency to surface bleeding, increases hemolysis and depresses erythrocyte production; also, in the presence of infection, erythrocyte survival time is

shortened.[13] Reduced levels of plasma transferrin and hypoferremia have been blamed. According to Stone,[14] the hematocrit may occasionally fall 10% to 20% over a 24-hour period in patients with large burns heavily infected with pseudomonas.

Assessment and Treatment of Anemia Following Thermal Burns

Before planning the volume of blood to be replaced, the physician must assess the depth of burning, based on the history of the accident and the appearance of the wound, as well as the size of the area burned. Blood is typed and cross-matched immediately. This must be done before administering dextran because this interferes with typing. At the same time samples must be drawn for hemoglobin, serum electrolytes, and blood urea nitrogen, in order to determine baseline values before treatment begins. Throughout treatment it is rarely necessary to use anything more than the patient's general condition and hemoglobin level as indications for, and guides to, the amount of transfusion.

The treatment plan followed at the Hospital for Sick Children is as follows.

Early Period (Up to 48 Hours After Burning)

During the first few hours after burning, the child's greatest need is for a non-colloidal electrolyte solution which will expand the intravascular volume, prevent hypovolemia and hemoconcentration, and maintain adequate peripheral perfusion. The more extensive the area of deep burn, the earlier blood should be given, but blood administered in the presence of hypovolemia and hemoconcentration, because it increases blood viscosity and decreases capillary blood flow, may cause further tissue damage. The kidneys are particularly liable to such injury because hemoconcentration and decreased urine production may produce renal tubular stasis, deposition of blood pigments and tubular obstruction.

In the early period, the disproportionate loss of plasma makes the hemoglobin values deceptively high. Only when the blood volume has been restored by plasma or plasma substitutes do hemoglobin levels accurately reflect the degree of anemia.

Blood is not given until the plasma volume has been expanded by solutions of electrolytes, or electrolytes and plasma expanders because plasma volume is lost faster and to a relatively greater extent than red blood cell volume.

Delayed Period (48 Hours to Two Weeks After Burning)

After the plasma volume has been restored, treatment should be aimed at keeping the hemoglobin level close to normal by replacing lost erythrocytes as soon as possible. When this is accomplished, further losses can be measured and replaced.

During the first three days we measure the hemoglobin level at least once every 12 hours; for the next three days we measure it once daily, and thereafter only every three to four days unless there is obvious blood loss. In early septicemia, gastrointestinal hemorrhage or continuing hemoglobinuria, the hemoglobin level must be monitored more closely.

Oral iron therapy is started as soon as the patient is taking a full diet. When the hemoglobin level falls to between 9 and 10 g./100 ml., if further blood loss is expected, or the nutritional state is poor we transfuse the patient. The hemoglobin level is always restored to at least 10 g./100 ml. before any operation.

The volume of blood to be given is calculated as follows:

$$\frac{\text{Hb. deficit in g./100 ml.}}{\text{Normal Hb. in g./100 ml.}} \times \text{normal blood volume in ml.}$$

The normal blood volume is estimated as 75 ml./kg. body weight. To avoid overloading the circulation we administer no more than 20 ml./kg. body weight at any one transfusion. However, if an episode of acute blood loss further reduces blood volume, this deficit should be made up as well.

Late Period (Two Weeks After Burning)

During this period the indications for transfusion are more flexible. If the patient's burns are almost healed, transfusion

may be withheld even if the hemoglobin level drops to as low as 9 g./100 ml., but if his general condition is poor, we may transfuse him when his hemoglobin level is between 10 and 11.5 g./100 ml.

During operations, the blood loss is measured and replaced. In rare cases this may mean giving up to as much as 50% of the normal blood volume.

Management of the Burned Child

We reviewed 109 randomly selected surviving thermal-burn patients admitted to the Hospital for Sick Children, Toronto, between 1952 and 1968; of these, 60 had suffered scald burns and 49 had flame burns. Of the flame burns, 28 (57%) required blood but only 11 (18%) of the scalded patients required blood transfusion. More of the flame-burned children needed transfusions because flame burns were usually deeper and larger; 62% of these burns involved more than 10% of the body surface while only 32% of the more superficial scald burns involved more than 10% of the body surface.

Every child who had a burn covering 30% or more of the body surface required blood transfusion. No patient with less than 5% body-surface burn required transfusion (Fig. 1). Older children required a greater volume of blood than infants and toddlers with burns over the same percentage of their body surface. In each child, the total volume of blood transfused throughout the course of burn treatment was approximately proportional to the percentage of the body surface burned. When these data are plotted against the ordinate "c.c. blood given" (instead of "blood transfused (c.c.)" as in Fig. 1), the scatter is even greater, *viz.* body surface area is not directly proportional to age. In a burned child, the surface area with second- and third-degree burns (expressed as a percentage) appears to provide the best single index of the need for blood.

The volume of blood transfused at one time varied from 100 c.c. in infants to 1000 c.c. in older children, and was most commonly 250 c.c. The number of transfusions per patient varied from one to 20, and was most commonly two (Fig. 2). Perhaps some of the single transfusions should have been withheld, but several of these were required to restore hemoglobin levels that had fallen to 8 or 9 g./100 ml. The patient who required 20 transfusions was hemorrhaging from an upper gastrointestinal ulcer. Blood transfusion was most frequently required during the first week after the burn, and was less likely to be needed each week thereafter (Fig. 3).

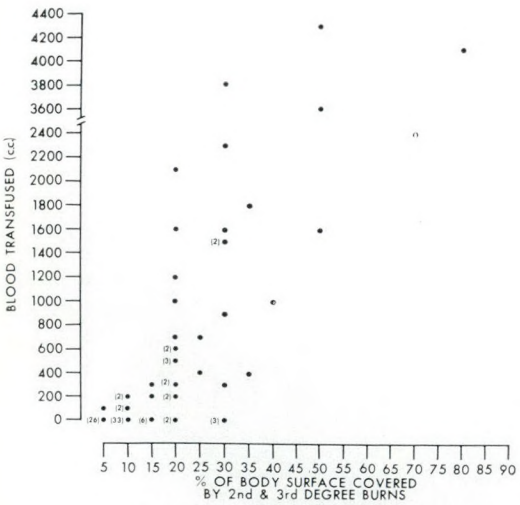

Fig. 1.—The volume of blood transfused is approximately proportional to the size of the burn. The number of patients represented by each dot is indicated by the number in brackets beside it.

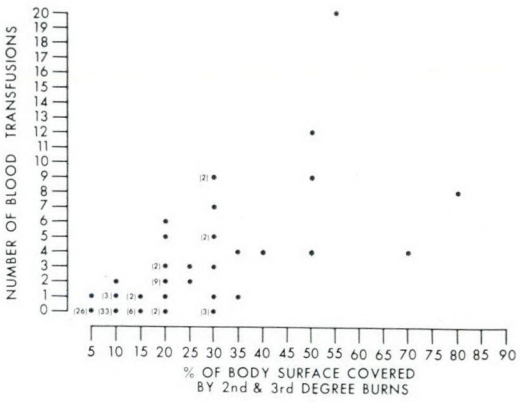

Fig. 2.—Shows the number of transfusions per patient. The number of patients represented by each dot is indicated by the number in brackets beside it.

In our survey we found that patients with widely varying pre-transfusion hemoglobin levels received blood because many

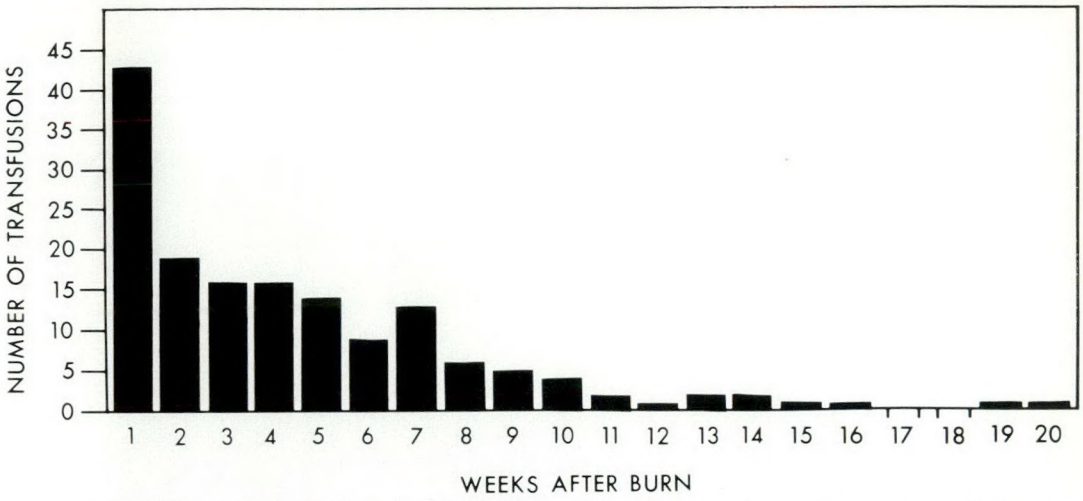

Fig. 3.—The relationship between the number of transfusions given to 39 patients and the time of their administration after burning.

transfusions were given at the time of operation. The volume given was calculated with a view to correcting preoperative anemia and replacing measured blood loss.

We found no correlation between the part of the body burned and the amount of blood transfusion required. The depth of the burn was important because only full-thickness burns bled profusely.

Summary

This paper briefly discusses some of the literature on burn anemia and reviews the management of 109 burned children at the Hospital for Sick Children in Toronto. Anemia in thermal burns results from trapping, damaging, and destruction of red blood cells in the burn wound, spontaneous and operative bleeding from the wound and skin donor area, depressed erythropoiesis due to burn infection, and gastrointestinal bleeding.

Blood transfusion requirements are approximately proportional to the total area of second- and third-degree burns. Blood administration is seldom indicated during the first few hours after burning when hypovolemia, due chiefly to plasma loss, should be corrected by colloidal plasma expanders and electrolyte solutions. Blood transfusion is required when the blood volume and urine production have returned to normal and the hematocrit has fallen below normal. Our review of blood transfusions in burned children shows this measure is most likely in the first week after burning and that transfusions decrease each week thereafter. Flame burns, which were usually larger and deeper than scald burns, more frequently produced anemia necessitating blood transfusion.

We wish to thank Mrs. Marilyn Morton, R.N., for her assistance in the clinical review included in this paper.

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Résumé

Le présent article passe brièvement en revue une partie de la littérature sur le sujet de l'anémie des brûlés et rouvre les dossiers de 109 enfants brûlés, qui ont été traités au Hospital for Sick Children de Toronto. L'anémie résultant d'une brûlure thermique est causée par la séquestration, la lésion et la destruction d'érythrocytes dans la plaie, par l'hémorragie spontanée ou opératoire à partir de la plaie et de la région greffée éventuelle, par une dépression de l'érythropoïèse d'origine infectieuse et par une hémorragie gastro-intestinale.

Les besoins de transfusions sont approximativement proportionnels à la superficie totale des brûlures du deuxième et du troisième degrés. Il est rare que la transfusion sanguine soit indiquée au cours des quelques heures qui suivent la brûlure: à ce moment, l'hypovolhémie causée principalement par la perte de plasma, se corrige mieux par l'administration de succédanés colloïdaux du plasma et de solutés électrolytiques. La transfusion de sang est nécessaire quand le volume de la masse sanguine et le débit urinaire sont normalisés et que l'hématocrite est descendue au-dessous de sa valeur normale. Nos observations sur les transfusions de sang chez le enfants brûlés montrent que cette mesure est surtout appliquée durant la première semaine après la lésion et que, par la suite, les besoins de transfusions diminuent régulièrement. Les brûlures par flamme vive qui sont généralement plus étendues et plus profondes que les échaudures causent plus souvent une anémie justiciable de transfusions.

FIBROMA FILLING THE RENAL PELVIS: REPORT OF A CASE

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Fibromas of the renal pelvis or calyceal system of the kidney are extremely rare. Only five such cases are recorded in the literature: in 1929 Boross[1] reported the first case; in 1949 Hüsch[2] described a myxoma of the pelvis which, it would appear, was a fibroma; in 1951 Immergut and Cottler[3] described the third—a young woman who, like the present case, complained of hematuria and flank pain; in 1963 Shucksmith[4] reported the fourth case, and in 1970 Bernier, Bédard and Narcisse[5] described a fifth.

Case Report

This young unmarried 29-year-old woman was seen in April 1969. Before being referred, she had had two episodes of painless hematuria, six and two months previously. Each episode had lasted some 12 hours, after which the urine had become clear to the naked eye. One week before referral, she developed severe colic, with pain radiating from the right loin to the right labium. This colic was accompanied by clots in the urine and lasted approximately 12 hours. After this last episode, she had a dull aching pain in the right loin.

She had some tenderness in the right renal angle, and the right kidney, which was readily palpable on inspiration, was quite tender. Her hemoglobin was 13.5 g./100 ml. and blood urea nitrogen was 25 mg./100 ml. Her urine showed some red blood cells on microscopy but was sterile.

An intravenous pyelogram (Fig. 1) showed a right hydronephrosis with loss of renal substance. The upper end of the ureter was pulled up, tortuous and dilated. The cause of this change was not demonstrated. Right renal function remained good. The left renal tract was normal. Cystoscopic examination was negative, but a retrograde pyelogram on the right side (Fig. 2) showed an irregular defect of the pelvis and upper end of the ureter. The responsible lesion seemed to extend into the middle third of the renal substance. The upper calyces were moderately dilated. This radiographic appearance suggested a renal tumour infiltrating the pelvis.

The right kidney was explored through a lumbar incision after excision of the twelfth rib. The kidney substance looked healthy; the pedicle and surrounding tissues were edematous; the pelvis was enlarged and dis-

*Box 329, Climax, Sask.

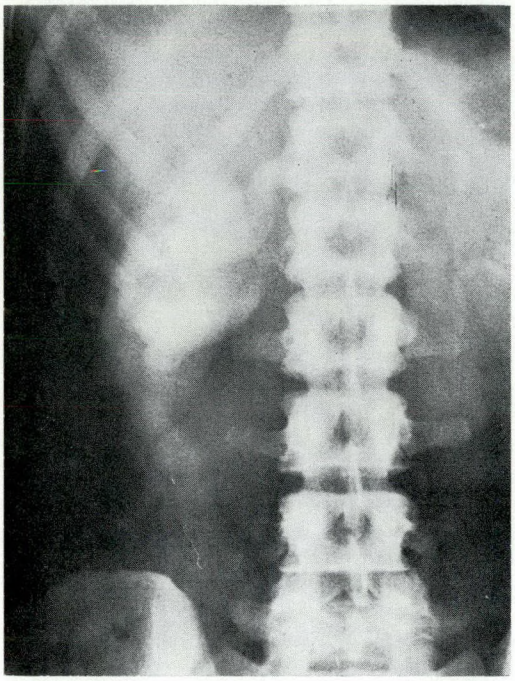

Fig. 1.—Intravenous pyelogram showing the abnormal right kidney.

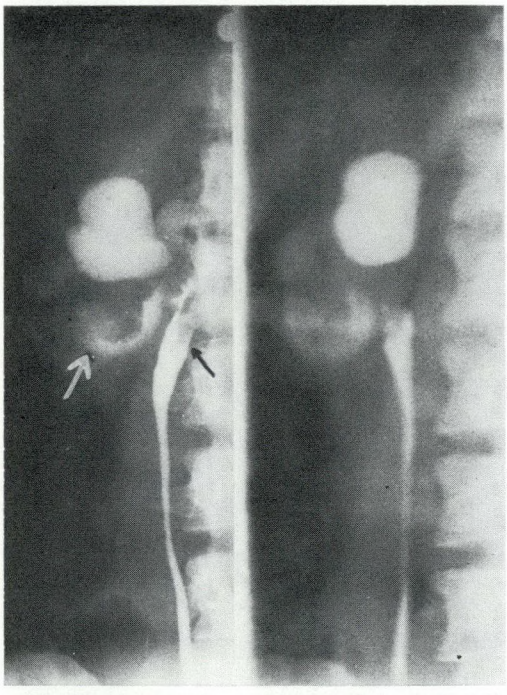

Fig. 2.—Retrograde pyelogram of the right kidney. The white arrow points towards the scalloped lower edge of the tumour as it lies inside the pelvis. The black arrow points to the lower limit of the tumour which has wormed its way into the ureter.

torted. On palpation, the pelvis was filled completely by a tumour which extended into the upper end of the ureter. The operative diagnosis was "papilloma of the pelvis"; a nephroureterectomy was done. This patient's postoperative course was uneventful.

The specimen (Fig. 3) consisted of a normal-sized kidney with its full length of ureter. The pelvis was distorted, enlarged, and filled completely with a velvety edematous mass which extended from the kidney to the upper end of the ureter. On bisecting the organ, it became obvious that the lesion was not a

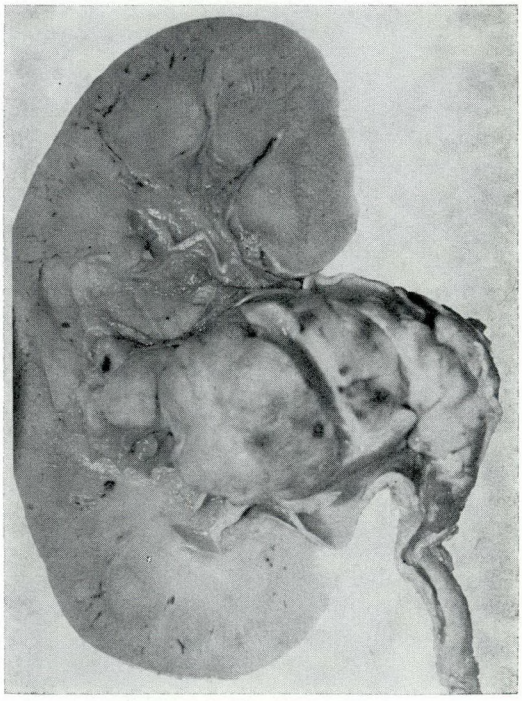

Fig. 3.—The bisected kidney.

papilloma. The homogeneous pale yellow tumour had taken the shape of the distorted pelvis and had pushed more than a centimetre into the upper ureter. It also extended into the middle calyx where it had its sole point of attachment. The other calyces were all moderately dilated.

On histologic examination (Fig. 4), the tumour was a fibroma of varying cellularity which showed considerable congestion. The pathologist commented that pure fibromas are rare in this site.

Discussion

Fibromas of the pelvis of the kidney are rare. Many authors of texts on tumours

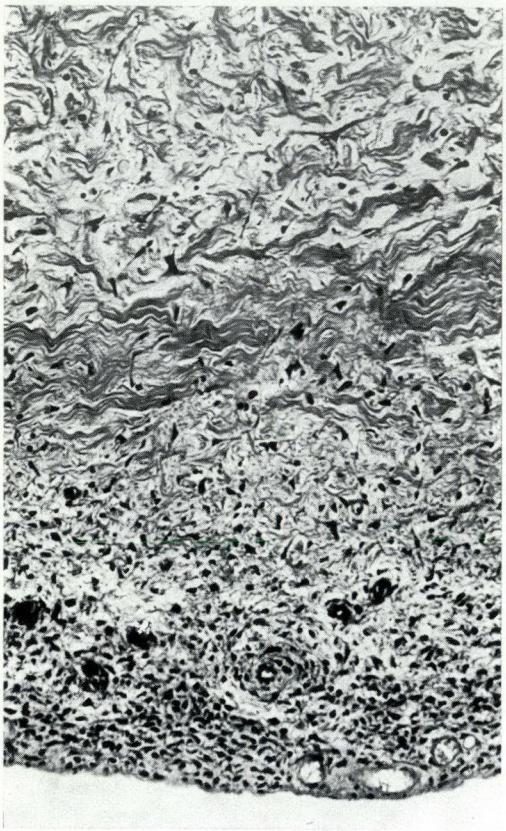

Fig. 4.—Photomicrograph showing the features of a fibroma.

of the urinary system do not even mention them. The lesion described here simulated the papillary tumour more commonly seen in this situation. Pyelotomy would have permitted a more accurate diagnosis, but would have carried a high risk of dissemination if the lesion had been a papillary carcinoma.

This tumour probably took origin from the mesenchymal tissue subjacent to the epithelium of the pelvis or calyceal system.

The lesions described by Boross,[1] Hüsch,[2] Immergut and Cottler,[3] Shucksmith,[4] and Bernier, Bédard and Narcisse[5] were attached to the pelvis; this lesion was attached by a pedicle to the middle calyx.

Summary

A young woman with hematuria had radiologic investigations which indicated that she had a lesion that occupied the pelvis of her right kidney. Exploration confirmed this. The tumour simulated the common epithelial and potentially malignant tumour in this area. Nephroureterectomy was performed. Histologically the lesion was a fibroma which originated from the middle calyx, filled and distorted the pelvis, and finally reached the upper end of the ureter.

The author wishes to thank Professor D. E. C. Mekie for providing a photograph of the bisected organ, which is now in the Royal College of Surgeons of Edinburgh Museum, and Dr. E. K. Dawson, Honorary Pathologist of the Museum for the histologic interpretation.

References

1. Boross E: Fibroma of renal pelvis. *Orv Hetil* 73: 1055, 1929
2. Hüsch P: Uber einen Fall von Myxom des Nierenbeckens. *Z Urol* 42: 286, 1949
3. Immergut S, Cottler ZR: Intrapelvic fibroma. *J Urol* 66: 673, 1951
4. Shucksmith HS: Fibroma of renal pelvis. *Brit J Urol* 35: 261, 1963
5. Bernier L, Bédard A, Narcisse R: Fibrome du bassinet. *Canad J Surg* 13: 315, 1970

Résumé

Chez une femme de 29 ans présentant de l'hématurie, la radiographie avait révélé une lésion occupant le bassinet du rein droit, confirmée par exploration. Cette tumeur simulait la tumeur épithéliale, potentiellement maligne, qui est courante dans cette région anatomique. On pratiqua une néphro-urétérectomie. A l'examen histologique, la tumeur était un fibrome qui avait pris naissance dans le calyce moyen, avait comblé et déformé le bassinet et avait finalement atteint l'extrémité supérieure de l'uretère.

BOOK REVIEWS

ANGIOLOGIE UND SZINTIGRAPHIE BEI KNOCHEN- UND GELENKERKRANKUNGEN. Vorträge anlässlich des 50. Deutschen Röntgenkongresses Stuttgart, 8.-11. Mai 1969. Edited by Rolf Glauner. 159 pp. Illust. Intercontinental Medical Book Corp., New York; Georg Thieme Verlag, Stuttgart, 1971. DM 48,00. $14.00 (approx.). Paperbound.

In the course of the German Radiology Congress in 1969, a conference was held on angiology and scintigraphy in bone and joint diseases, because the techniques of angiology can be applied to the diagnosis of a number of skeletal diseases. The increased vascularization of a primary or metastatic bone tumour can be demonstrated but similar AV shunts develop in acute and subacute osteomyelitis. Therefore, the procedure is not diagnostic but may provide valuable information about the extent of a tumour. In femoral head necrosis, the deficient blood supply can be demonstrated with angiography. Venography has been used to assess the blood supply of the proximal fragment in fractures of the neck of the femur. The contrast medium is injected into the femoral head and the adequacy of the venous drainage can then be assessed. If the veins are intact, it may be assumed that the arteries are intact too. Scintigraphy demonstrates radioactive isotopes in localized areas after the injection of a radio-pharmaceutical agent, usually radioactive strontium. The isotope is deposited in areas of increased bone formation which may be physiologic, as in the epiphysis of children, or pathologic. A pathologic process may be detected before bone destruction becomes evident on radiography. Increased deposition of radioactive strontium has been demonstrated in the course of fracture healing.

Probably only a few physicians and surgeons are aware of the diagnostic value of these procedures. This monograph presents the current state of the art well, including its limitations.

ANTIKOAGULANTIEN- UND FIBRINOLYSETHERAPIE. Jürgen Jaenecke. 158 pp. Illust. Intercontinental Medical Book Corp., New York; Georg Thieme Verlag, Stuttgart, 1971. DM 8,00. $2.20 (approx.). Paperbound.

This monograph describes the present state of the art in a clear and concise manner. The first chapter, devoted to a discussion of the modern theories of blood coagulation and fibrinolysis, describes the principles and the pharmacology of anticoagulants and of the antagonists of the anticoagulants. Laboratory methods used to diagnose disturbances of the

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THE CANADIAN JOURNAL OF SURGERY

All communications concerning this journal should be marked "The Canadian Journal of Surgery" and addressed to the Editor, 530 Scarlett Road, Suite 1002, Weston 626, Ont.

The Journal is published bi-monthly. Subscription is $15 per year ($7.50 per year for trainees in surgery), and starts with the January issue of each year. Single copies are $2.50 each, payable in advance. (It would be greatly appreciated if subscribers would add bank exchange to their cheques.)

INSTRUCTIONS TO CONTRIBUTORS

Manuscripts

Manuscripts **in duplicate** of original articles, case reports, and other contributions should be forwarded with a covering letter requesting consideration for publication in *The Canadian Journal of Surgery*. Acceptance is subject to the understanding that they are submitted solely to this Journal, and will not be reprinted without the consent of the author and the publishers. Acceptance or rejection of contributions will be determined by the Editorial Board. As space is available, a limited number of case reports will be published. Articles should be typed on one side only of unruled paper, double-spaced, and with wide margins. The author should always retain a carbon copy of material submitted. Every article should contain a summary of the contents. The Concise Oxford Dictionary will be followed for spelling. Dorland's Illustrated Medical Dictionary will be followed for scientific terminology. The Editorial Board reserves the right to make the usual editorial changes in manuscripts, including such changes as are necessary to ensure correctness of grammar and spelling, clarification of obscurities or conformity with the style of *The Canadian Journal of Surgery*. In no case will major changes be made without prior consultation with the author. Authors will receive galley proofs of articles before publication, and are asked to confine alterations of such proofs to a minimum.

Reprints

Reprints may be ordered on a form which will be supplied with galley proofs. It is important to order these before publication of the article, otherwise an extra charge for additional type-setting will be made.

References

References should be referred to by numerals in the text. They should include in order: the author's name and initials in capitals, title of the article, abbreviated journal name, volume number, page number and year. The abbreviations of journal names should be those used in *Index Medicus*. References to books should include in order: author's name and initials, title of book, number of edition (e.g. second ed.), city of publication, title of publishing house, year of publication, page number if a specific reference. For examples, see this journal January 1971 issue onwards.

Illustrations

A reasonable number of black-and-white illustrations will be reproduced free with the articles. Colour work can be published only at the author's expense. Photographs should be glossy prints, unmounted and untrimmed, preferably not larger than 8″ x 6″. Prints of radiographs are required and *not the originals*. The magnification of photomicrographs must always be given. Photographs must not be written on or typed on. An identifying legend may be attached to the back. Patients must not be recognizable in illustrations, unless the written consent of the subject for publication has been obtained. Graphs and diagrams should be drawn in India ink on suitable white paper. Lettering should be sufficiently large that after reduction to fit the size of the Journal page it can still be read. Legends to all illustrations should be typed separately from the text and submitted on a separate sheet of paper. Illustrations should not be rolled or folded.

Language

It should be clearly understood that contributors are at full liberty to submit articles in either English or French, as they please. Acceptance will be quite independent of the language of submission. If the contributor wishes, he may submit an informative summary of not more than 300 words in the language other than that in which he has submitted the article. For example, an article in English must carry an English summary and may, if the author wishes, carry a more detailed summary in French.

(Continued from p. 353)

blood coagulation and to monitor anticoagulant therapy are presented in detail as well as the clinical indications, contraindications and complications. The last paragraphs cover thrombolysis, again including laboratory methods, and clinical application. This book, which is written for practitioners, does not go into details regarding the controversial aspects of this type of treatment, for instance, the use of anticoagulants in the prevention and treatment of myocardial infarction.

CARDIOVASCULAR SURGERY 1969. Council on Cardiovascular Surgery, American Heart Association, Scientific Sessions, Dallas, Texas, November 13-16, 1969. American Heart Association Monograph Number 30. Edited by Earle B. Mahoney. 178 pp. Illust. The American Heart Association, Inc., New York, 1970. $5.00. Paperbound.

This monograph, published by the American Heart Association, consists of 28 papers selected from the presentations at the Cardiovascular Surgical Section of the 1969 scientific sessions of the American Heart Association (Dallas, Texas, November 13-16, 1969). As one would expect, cardiac transplantation appears to be dormant and no clinical papers on this topic were submitted. Basic experimental work in this area continues, and the modern methods of organ preservation are well presented in two papers. The problems of cardiac valvular replacement (prosthetic, heterograft and homograft) account for the largest number of papers on any one topic presented at this meeting.

The surgery of coronary artery disease is considered in several papers and the exciting new field of direct coronary surgery is well represented with two papers, one using the saphenous vein and the other the internal mammary artery.

Congenital heart disease and its current surgical treatment are covered. Peripheral vascular disease, artificial cardiac assistance and the metabolic problems of cardiac surgery are not neglected.

This book will be used most by cardiologists and cardiovascular surgeons, but it belongs on the shelf of any medical library where knowledge is sought on the current status of cardiovascular surgery.

COMPLICATIONS OF ANESTHESIA. Compiled and edited by Lawrence J. Saidman and Frank Moya. 298 pp. Illust. Charles C Thomas, Publisher, Springfield, Ill., 1970. $12.75.

This book contains the proceedings of the postgraduate seminar in anesthesia sponsored by the University of Miami, Florida. Well edited, this is a text that anesthesiologists will

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LE JOURNAL CANADIEN DE CHIRURGIE

Toute communication concernant le Journal devra porter la mention "Le journal canadien de chirurgie" et être adressée à l'Editeur, 530 Scarlett Road, Suite 1002, Weston 626, Ont.

Le journal est publié à tous les deux mois. Le prix de l'abonnement est de $15. par an ($7.50 par an pour les médecins qui sont résidents en chirurgie) et commence avec le numéro de janvier de chaque année. Un exemplaire isolé coûte $2.50 et est payable d'avance. (Nous serions reconnaissants aux souscripteurs de vouloir bien ajouter à leur chèque le montant des frais bancaires éventuels).

INSTRUCTIONS A NOS COLLABORATEURS

Manuscrits

Les manuscrits d'articles originaux, de rapports cliniques etc. seront envoyés en deux exemplaires, accompagnés d'une lettre demandant qu'on veuille bien considérer leur publication dans *Le journal canadien de chirurgie.* Ils ne seront acceptés qu'à la condition qu'ils n'aient été soumis qu'à notre Journal et qu'ils ne soient pas réimprimés sans le consentement exprès de l'éditeur et l'auteur. L'acceptation ou le refus des articles soumis relève du Conseil de la publication. Si la place est disponible, un nombre limité d'histoires cliniques pourront être publiés. Les articles seront dactylographiés sur un seul côté d'un papier non ligné, à double espace et avec une large marge. L'auteur devra toujours conserver une copie au papier carbone du texte soumis. Tout article devra être accompagné d'un résumé. L'orthographe sera celle adoptée par le dictionnaire Larousse. Quant à la terminologie scientifique, elle sera basée sur le Dictionnaire des termes techniques de médecine ou tout autre ouvrage de référence sérieux. Le Conseil de la publication se réserve le droit d'apporter au texte les changements qu'il jugerait à propos pour assurer la correction grammaticale et l'orthographe, pour éliminer d'éventuelles obscurités ou pour rendre la présentation conforme au style du *Journal canadien de chirurgie.* Aucun changement important ne sera apporté au texte sans que l'auteur aît été préalablement consulté. Les auteurs recevront avant la publication des épreuves d'imprimerie de leur texte, auxquelles ils sont priés d'apporter le minimum de corrections.

Tirés-à-part

On pourra commander des tirés-à-part sur une formule qui est envoyée avec les épreuves. Il est important de les commander avant la publication de l'article, sous peine de devoir payer un supplément pour une nouvelle composition.

Bibliographie

Les références bibliographiques seront indiquées par des numéros dans le corps du texte. Elles comprendront dans l'ordre: le nom de l'auteur et ses initiales, en majuscules, le titre abrégé du Journal, le numéro du volume, le numéro de la page et l'année. Les abréviations admises pour les noms de revues sont celles qui figurent dans *l'Index Medicus.* Les renvois aux livres comprendront dans l'ordre: le nom de l'auteur, ses initiales, le titre de l'ouvrage, le numéro de l'édition (p. ex. deuxième éd.), la ville et le nom de la maison d'édition, et l'année de la publication; enfin, le numéro de la page s'il s'agit d'un renvoi précis. Pour examples, voyez l'issue de janvier 1971 et ceux à venir.

Illustrations

Le journal accepte de publier gratuitement un nombre raisonnable d'illustrations en noir et blanc. Les reproductions de clichés en couleurs seront publiées aux frais de l'auteur. Les photographies seront imprimées sur papier brillant, ne seront ni montées ni calibrées et d'un format maximum de 6″ x 8″. En ce qui concerne les radiographies, nous demandons des copies et *non pas l'original.* On devra toujours fournir un agrandissement de microphotographies. Il ne faut jamais écrire ou dactylographier un texte quelconque sur les photographies. Une légende les identifiant pourra être jointe au dos. Dans les illustrations montrant des malades, ceux-ci ne pourront être reconnus, à moins qu'ils n'en aient donné le consentement écrit préalablement à la publication. Les graphiques et diagrammes seront dessinés à l'encre de Chine sur un bon papier à dessin blanc. Le lettrage devra être écrit en caractères assez grands pour que, aprè réduction proportionnelle au format du Journal, ils soient encore lisibles. Les légendes devant accompagner les illustrations seront dactylographiées sur une feuille indépendante du texte. Les illustrations ne seront ni roulées ni pliées.

Langue véhiculaire

Il doit être clairement établi que les collaborateurs ont pleine liberté de soumettre leurs articles en français ou en anglais, à leur choix. L'acceptation de l'article sera entièrement indépendante de la langue choisie par l'auteur. Si le collaborateur le désire, il peut décrire le contenu de l'article en un sommaire ne dépassant pas 300 mots et dans une langue différente de la langue choisie pour l'article lui-même. Par exemple, un article écrit en français doit comporter un résumé en français et peut, si l'auteur le désire, être accompagné d'un sommaire plus détaillé en anglais.

(Continued from Adv. p. 21)

find well worth reading. However, its title gives the reader a wrong impression of its content. Presented clearly but briefly are reviews by outstanding authorities on the advances made in specific areas of the specialty. Acquisition of this knowledge has brought with it a better understanding of how best we can recognize and treat complications if and when they arise. Of extreme interest to this reviewer was the section devoted to the medicolegal aspects presented by several eminent lawyers in the United States. This section should be read by all anesthetists and surgeons who are involved in the management of patients undergoing surgery. Several well-prepared chapters deal with some heretofore little-known subjects—genetics, congenital malformations in children, enzyme induction and molecular disease.

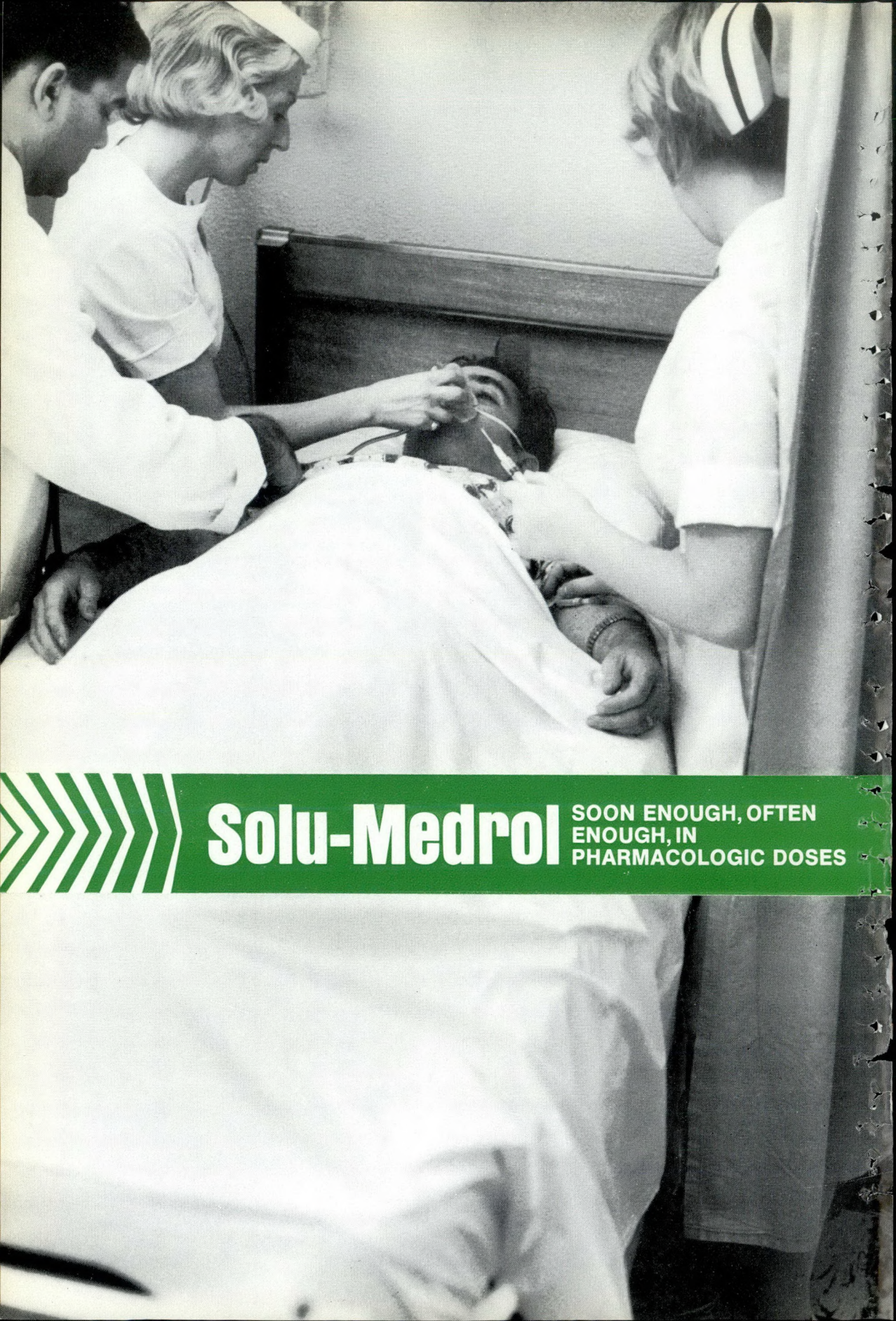
The editors have provided an understandable text which should prove to be a welcome addition to the armamentarium of the practising anesthesiologist.

THE CONTINUING EDUCATION OF THE SURGEON. Transactions of the 12th Annual Meeting of The Allen O. Whipple Surgical Society. Edited by Harold G. Barker. 121 pp. Illust. Charles C Thomas, Publisher, Springfield, Ill., 1971. $11.75.

This little book contains the transactions of the 12th Annual Meeting of the Allen O. Whipple Surgical Society, which addressed itself to the problem of continuing education. It describes the Albany Regional Hospital Program, a two-way radio-linked program of the Medical Center and several surrounding community hospitals. There is a description of the educational activities of the American College of Surgeons, a discussion of university Departments of Education, and a brief discussion of the material that should be contained in a continuing educational activity. The role of the American Board, the use of tumour registry, and a discussion of the motivation of scientists for continuing education are also in this book.

Perhaps the most significant chapter deals with the use of non-affiliated hospitals for continuing education, and only this chapter provides a discussion of the mechanisms of learning and some of the problems of continued learning. Most of the book concerns itself with the teaching facet of the teaching-learning axis, and there is no analysis of the problems of learning, the identification of curriculum, or means of evaluation or assessment. It fails to come to grips with the objectives of continuing education, the specific means whereby education may occur, and some assessment or evaluation as to whether or not it has happened.

(Continued on Adv. p. 26)



Solu-Medrol

SOON ENOUGH, OFTEN ENOUGH, IN PHARMACOLOGIC DOSES

(Continued from Adv. p. 29)

This book will prove useful to the resident commencing his training, or the specialist practising without the benefit of an extensive library.

TOXOPLASMOSE. PRAKTISCHE FRAGEN UND ERGEBNISSE. Edited by Heinz Kirchhoff and Heinrich Langer. 83 pp. Illust. Intercontinental Medical Book Corp., New York; Georg Thieme Verlag, Stuttgart, 1971. DM 26,00. $7.60 (approx.). Paperbound.

The present problems of toxoplasmosis are reviewed in this short 81-page monograph. Prenatal infection may lead to abortion or to lesions in the central nervous system. Postnatal infection can occur following ingestion of uncooked infected meat (beef and pork) or through contamination of food with the excreta from infected cats. The life cycle of the parasite seems to be well established; many wild and domesticated animals can be infected and may pass the infection on to man. The clinical incidence and the clinical manifestations of the disease still appear to be unclear and it is difficult to evaluate the clinical significance of toxoplasmosis. Animal experiments are reported in some detail, suggesting that the book is aimed primarily at investigators rather than practitioners.

THE TREATMENT OF BURNS. Principles and Practice. William W. Monafo. 267 pp. Illust. Warren H. Green, Inc., St. Louis, 1971. $15.00.

In his preface, the author states that this book is written for students, house officers and for physicians who must occasionally treat burned patients. This goal is lost sight of in several sections of the publication.

Statistical and historical data on burns and their treatment are well presented. Too much emphasis is placed on the treatment of burn shock with hypertonic lactated saline solution as used by the author, as opposed to the regimens for resuscitation used by other burn centres.

Topical therapy of the burn wound with antimicrobial agents is the most recent major advance in the treatment of thermal injuries. The author is obviously impressed with the use of silver nitrate as a topical agent and stresses its use too strongly considering the aims of the book.

The remainder of the work describing operative methods, rehabilitation, complications and their treatment is well presented.

This is an acceptable text which will be of use to medical students and interns as an easily readable reference book.

Books Received

Books are acknowledged as received, but in some cases reviews will also be made in later issues.

Angiologie und Szintigraphie bei Knochen- und Gelenkerkrankungen. Vorträge anlässlich des 50. Deutschen Röntgenkongresses Stuttgart, 8.-11. Mai 1969. Edited by Rolf Glauner. 159 pp. Illust. Intercontinental Medical Book Corp., New York; Georg Thieme Verlag, Stuttgart, 1971. DM 48,00. $14.00 (approx.). Paperbound.

Campbell's Operative Orthopaedics. 2 vols. 5th ed. Edited by A. H. Crenshaw. 2044 pp. and indexes. Illust. The C. V. Mosby Company, St. Louis, 1971. $83.50.

Cardiovascular Surgery 1970. Council on Cardiovascular Surgery, American Heart Association, Scientific Sessions, Atlantic City, New Jersey, November 12-15, 1970. American Heart Association Monograph Number 34. Edited by Earle B. Mahoney. 158 pp. Illust. The American Heart Association Inc., New York, 1971. $5.00. Paperbound.

Coronary Heart Disease. International Symposium in Frankfurt, January 22-24, 1970. Edited by Martin Kaltenbach and Paul Lichtlen. 269 pp. Illust. Intercontinental Medical Book Corp., New York; Georg Thieme Verlag, Stuttgart, 1971. DM 39,00. $11.40 (approx.). Paperbound.

The Hand. Lee Milford (from the 5th edition of Campbell's Operative Orthopaedics, edited by A. H. Crenshaw). 282 pp. Illust. The C. V. Mosby Company, St. Louis, 1971. $20.50.

Handbook of Obstetrics & Gynecology. 4th ed. Ralph C. Benson. 774 pp. Illust. Lange Medical Publications, Los Altos, California, 1971. $6.50. Paperbound.

Immunologie. Ein Lernprogramm für Studierende und Arzte. Jean Lindenmann. 275 pp. Illust. Intercontinental Medical Book Corp., New York; George Thieme Verlag, Stuttgart, 1971. DM 19,80. $5.80 (approx.). Paperbound.

Pathologische Anatomie. Vol. 1. Allgemeine Pathologie. 3rd ed. Hans Ulrich Zollinger. 336 pp. Illust. Intercontinental Medical Book Corp., New York; Georg Thieme Verlag, Stuttgart, 1971. DM 12.80. $3.75 (approx.). Paperbound.

Pathology of Tumours of the Nervous System. 3rd ed. Dorothy S. Russell and Lucien J. Rubinstein. 429 pp. Illust. Edward Arnold (Publishers) Ltd., London; The Macmillan Company of Canada Limited, Toronto, 1971. $32.75.

A Practice of Thoracic Surgery. 3rd ed. A. L. d'Abreu, J. Leigh Collis and D. B. Clarke. 652 pp. Illust. Edward Arnold (Publishers) Ltd., London; The Macmillan Company of Canada Limited, Toronto, 1971. $49.50.

Simultaneous Prostatectomy and Inguinal Herniorrhaphy. Sidney R. Weinberg, Albert Kovetz and Stephen M. Lazarus. 51 pp. Illust. Charles C Thomas, Publisher, Springfield, Ill.; McGraw-Hill Company of Canada, Toronto, 1971. $8.00.

Surgeon's Decisions. H. L. Duthie. 112 pp. Illust. Oliver and Boyd, Edinburgh, 1971. Price not stated. Paperbound.

Toxoplasmose. Praktische Fragen und Ergebnisse. Edited by Heinz Kirchhoff and Heinrich Langer. 83 pp. Illust. Intercontinental Medical Book Corp., New York; Georg Thieme Verlag, Stuttgart, 1971. DM 26,00. $7.60 (approx.). Paperbound.

NOTICES

CANADIAN ASSOCIATION OF PAEDIATRIC SURGEONS

The Fourth Annual Meeting of the Canadian Association of Paediatric Surgeons will be held in Toronto, Ontario, on January 26 and 27, 1972.

For information concerning this meeting, please write to: Dr. Barry Shandling, Suite 1120, 123 Edward Street, Toronto 101, Ontario.

AMERICAN COLLEGE OF SURGEONS CLINICAL CONGRESS

The 57th annual Clinical Congress of the American College of Surgeons will be held in Atlantic City from October 18-22, 1971.

Features of the meeting will include 17 postgraduate courses given for younger surgeons by widely experienced teachers; more than 45 panel discussions and symposia on current problems in general surgery and surgical specialties by experts in the field; a review of "What's New" in surgery; closed-circuit telecasts of actual operations from the Thomas Jefferson University Hospital, Philadelphia; approximately 450 scientific sessions and industrial exhibits; special sessions dealing with cancer, trauma, and undergraduate surgical education; a general session on professional liability and one on the Surgical Education and Self-Assessment Program of the College which was designed to help Fellows (members) and other qualified physicians evaluate the extent of their basic clinical knowledge in surgery.

Major addresses will be given during the week by the incoming President, Dr. J. E. Rhoads, Dr. W. A. Altemeier, Dr. R. A. Good, Dr. P. Handler and Dr. C. A. Berry.

A new feature on the College program will be a John H. Gibbon, Jr. lecture by M. E. DeBakey, President of Baylor College of Medicine, Houston.

For further information contact Sara Barr Cohen, Director of Publicity, American College of Surgeons, 55 East Erie Street, Chicago, Illinois 60610.

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