Circulatory and Metabolic Alterations Associated with Survival or Death in Peritonitis:

Clinical Analysis of 25 Cases

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DIFFUSE purulent peritonitis remains a life endangering situation [11, 13] despite advances in therapy based upon sound observations of the associated physiologic and biochemical derangements.[10, 42] Much is known of the early fluid [11, 30] and electrolyte derangements [7, 14] in developing extensive inflammation.[6, 21] The frequently associated respiratory failure [5, 24, 38] and the extensive caloric energy expenditure accompanied by nitrogen loss [25, 32] are understood as cause for exhaustion. The pathogenesis and lethal effects of renal shut-down have been described.[31, 35, 42] Hemodynamic measurements in septic or hypovolemic shock elucidate the initial metabolic disorders,[7, 27, 39] yet little information is available concerning the circulatory requirements for early or late survival from the hazardous condition of widespread peritoneal infection.

It is the purpose of this paper to present observations on the relationship of the cardiac output and the circulatory function to the metabolic state of patients suffering from spreading infectious peritonitis. From these data it is possible to appreciate the importance of the transport system in this dangerous situation. The interdependence of the various organ systems, including the endocrines, becomes apparent in the maintenance of cellular metabolic activity throughout the body.

When considering the effects of fulminating peritonitis, it is convenient to divide its course into three phases: 1) inadequate circulation and a metabolic state of shock associated with hypovolemia, electrolyte shifts [11, 28, 30] and bacteremia; [27, 40] 2) control of the septic process and the establishment of an inflammatory barrier; this leads to early recovery or 3) prolonged intra-abdominal sepsis, requiring drainage of multiple abscesses or correction of intestinal defects.[42] This third period is the time of extreme wasting [25] and may lead ultimately to exhaustion and death.[10, 31] Whereas little more than the resting basal cardiac output is required for an uncomplicated recovery from a major operation,[7, 9] survival in the presence of sepsis and inflammation demands a considerable and sustained increase of circulation.[1] It appears that the same is true in extensive peritonitis. When this requirement is not satisfied for any

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cause, as long as the inflammatory process is present, progressive loss of cellular energy production and organ function follow. Acidosis and death are the inevitable sequence unless corrective measures can be applied. These observations amplify the need for certain therapeutic methods and emphasize their importance.

Clinical Analysis

Twenty-five patients with evidence of fulminating peritonitis were selected for study from the wards of the Medical College Hospital in Charleston, South Carolina, and the Cleveland Metropolitan General Hospital in Cleveland, Ohio. Suffering from a variety of causes for peritonitis, usually a perforated hollow viscus, patients are listed in the first columns of Tables 1, 2, and 3. Ages ranged from 11 to 80 years. Seven patients who were studied are not included in this report since they had localized intra-abdominal abscesses which merely required drainage. All but two of the 25 patients were ultimately operated upon. Diagnoses in these two (#20 and #21, Table 3) were confirmed at autopsy.

Initial treatment was restoration of fluid volume employing isotonic saline solution, whole blood, or glucose solution guided by hematocrit and electrolyte values. Later in the series, measurements of central venous pressure assisted in determining fluid requirements. A variety of antibiotics were employed in large doses, nearly always including penicillin (1,000,000 units every 6 hours) and streptomycin (2 Gm. daily). Other chemotherapeutic agents were used as indicated when culture results were returned. Following rehydration and stabilization of the patient's clinical state an operation under general anesthesia was undertaken for removal or exteriorization of the perforated viscus. In other instances, as will be pointed out, drainage only was effected. In six patients mechanical ventilators were employed through cuffed endotracheal or tracheostomy tubes for periods up to 8 days. Cooling to nearly normal body temperature was accomplished by externally applied hypothermic blankets when fever more than 38.3° C. persisted. Patients who did not respond to these measures and continued in a state of shock were given hydrocortisone in doses of 200 to 300 mg. every 8 hours.

Methods and Procedure

The hemodynamic and metabolic observations employed methods detailed in previous publications.[7, 8, 9] In brief, plastic catheters with stopcocks were introduced into the radial artery and the antecubital vein by means of a small incision, if necessary. The catheters were filled with a dilute solution of heparin in isotonic saline at times when they were not in use. By this means patency could be maintained from 4 to 7 days. Cardiac outputs were measured by dye dilution curves employing indocyanine green.[15] To permit comparison from patient to patient, the cardiac output values were converted to cardiac indices. Arterial blood pressure was recorded by a cuff, if possible. Otherwise, a mean arterial pressure was obtained by means of a calibrated strain gauge attached to the arterial catheter. Central venous pressure from the superior vena cava or right atrium was measured with a saline manometer. To ensure comparable values, the zero point of the manometer was placed at the mid-axillary line, the estimated level of the right atrium, when the patient was in the supine position.

At the time of each hemodynamic observation, an arterial blood sample was obtained for determination of pH, buffer base, pCO_2,[2] lactate,[3] pyruvate,[16] and electrolyte values. The latter included plasma sodium, potassium, chloride and blood urea nitrogen. In eight patients data are available on the daily excretion of cortisol in the urine.[37]

TABLE 1. *Peritonitis—*

Case No.	Age Diagnosis	Initial CI.	Initial CVP. BP.	Initial pH	Initial ΔBB	Initial Lact. Pyr.	Posttreatment CI.	Posttreatment CVP. BP.	Posttreatment pH	Posttreatment ΔBB	Posttreatment Lact. Pyr.
(1)	53 WF Subhepatic abscess spread	4.4	13 146/80	7.44	+3	10/3	3.8	140/80	7.40	−2	20/5
(2)	36 WM Obstruction; perforation bowel						3.7	4 100/65	7.36	+3	17/3
(3)	60 CM Leak; duodenal stump	2.7	3.0 68/50	7.32	−6	28/5	4.6	5 96/72	7.38	−4	20/4
(4)	39 CF Perforation of uterus; hysterectomy						1.5	0 102/60	7.50	−4	58/11
(5)	39 CM Perforated appendix	3.5	— 110/80	7.37	−7	23/4	4.0	— 99/60	7.32	−8	—
(6)	19 CM Perforated appendix; diabetes						3.5	5 146/72	7.35	−8	—
(7)	58 CM Colon obstruction; perforated cecum										
(8)	80 WM Ca. colon; rupture	2.3	5 110/78	7.59	+3	13/3	3.2	3.5 122/70	7.44	−1	34/5
(9)	39 WM Perforated peptic ulcer (6 hr.)	3.0	2 110/60	7.36	−4	22/5	3.0	7 105/60	7.34	−6	20/4
(10)	63 WM Perforated diverticulum colon	4.2	4 125/75	7.36	−3	18/4					
(11)	11 CM Obstruction; gangrene ileum	1.5	−2 80/50	7.28	−15		3.2	7 120/70	7.32	−10	
(12)	57 WM Perforated peptic ulcer (11 hr.)	1.8	2 90/55	7.31	−12	54/7	1.7	13 85/55	7.34	−9	49/6

When it had been determined that a patient was suffering from extensive peritonitis, catheters were introduced into the vessels. An observation was made as soon as possible. In 13 patients this was accomplished prior to the operation. However, each had received some fluid, one liter or more, prior to this time. Serial observations were made after the operation and at daily intervals thereafter. If a major change of therapy such as the introduction of a mechanical ventilator was to be instituted, an attempt was made to obtain an observation before and after the patient had become stabilized on the new regime.

Body weights were recorded at intervals

Prompt Recovery

Day 1					Day 2–4					Day 5–7				
CI.	CVP. BP.	pH	ΔBB	Lact. Pyr.	CI.	CVP. BP.	pH	ΔBB	Lact. Pyr.	CI.	CVP. BP.	pH	ΔBB	Lact. Pyr.
														Drainage
4.4	3 112/72	7.40	+3	15/6	3.4	4 110/60	7.46	+7		3.3	3 100/58	7.35	0	7/2
3.0	0 120/60	7.32	−3	43/8	3.5	11 140/70	7.51	+6	27/5	3.1	12 130/68	7.52	+7	20/4
4.0	0 99/60	7.32	−5	19/3	3.1	— 130/90	7.36	−3	13/3					
2.1	13 124/72	7.42	−1	—	3.6	12 126/68	7.48	+3	—	3.2	6 124/62	7.44	+3	—
3.3	6 120/96	7.44	+1	10/4	3.1	12 130/100	7.43	0	6/2					
					2.8	3 148/80	7.45	+7	9/2	2.8	4 128/70	7.52	+9	17/3
					4.1	5 115/65	7.44	0	14/3	3.1	6 120/70	7.42	+1	15/3
3.8	6 132/80	7.42	−2	14/3	3.6	6 135/80	7.41	−2	12/2					
3.0	6 110/68	7.36	−6		4.2	4 125/80	7.38	−2		3.1	4 120/70	7.40	0	
4.1	6 124/76	7.43	−3	20/4	3.2	6 115/70	7.44	−5	24/5	3.6	4 120/65	7.42	+3	16/3

when practical. Fluid intake and urinary output were also followed. The majority of the studies were carried out in the Intensive Care Unit.

Results

Of the 25 patients with generalized infectious peritonitis, 16 survived and nine died. Among the survivors, 12 had uneventful convalescences following control of the source of the peritoneal contamination and are classed as "Prompt Recovery" (Table 1). Four patients underwent prolonged convalescence due to secondary abscesses or intestinal fitulas and are classed as "Late Recovery" (Table 2).

TABLE 2. *Peritonitis—*

Case No.	Age Diagnosis	Initial CI.	Initial BP.	Initial CVP.	Initial pH	Initial BB	Initial Lact. Pyr.	Day 1–2 CI.	Day 1–2 BP.	Day 1–2 CVP.	Day 1–2 pH	Day 1–2 BB	Day 1–2 Lact. Pyr.
(13)	64 CM Appendicitis; perforated	1.6	90/50	−3	7.42	−4	18/3	2.2	100/60	2	7.43	−5	22/3
(14)	15 WM Liver & subhepatic abscess	4.0	120/90	2	7.33	−3	32/6	6.1	124/70	7	7.51	+8	14/4
(15)	11 CM Appendicitis; perforated	2.5	96/86	4	7.31	−9	59/12	4.1	100/60	15	7.47	5	13/3
(16)	61 WM Appendicitis; perforated	2.6	95/65	−1	7.28	−10	38/7	3.3	110/65	8	7.44	−2	24/4

The values from the patients who died are detailed in Table 3. These patients are listed according to their responses and the time of death: 1) "Acute Deaths," 2) "Delayed Death," 3) "Late Deaths." This permits ready comparison between the failure of compensation which resulted in death and the state of the survivors at the various stages of the illness.

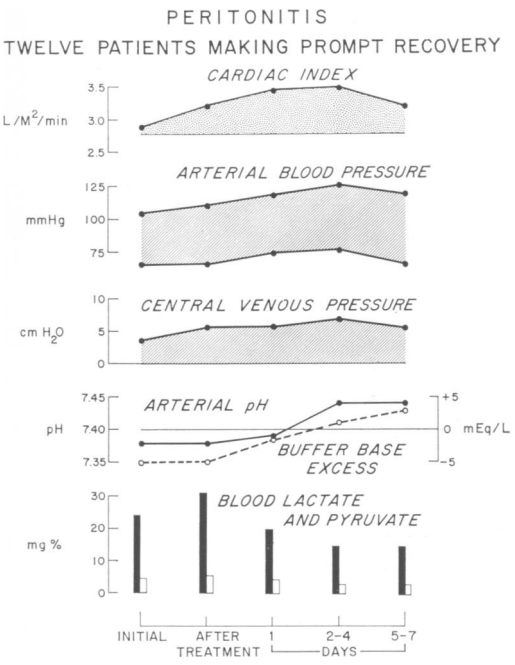

FIG. 1. Average values obtained from 12 patients who made "Prompt Recoveries" from peritonitis. Note elevated cardiac indices during the first week and relatively normal metabolic state of these patients.

Prompt Recovery. A general similarity exists in the responses of those patients who recovered without incident after the initial bacterial insult to the peritoneum was controlled. Average values are presented in Figure 1. In the middle of the first week the cardiac index was 3.5 L./M.²/min. This index is 125% of the normal resting value, which is approximately 2.8 L./M.²/min. Five patients during this time maintained very high outputs of 4 L./M.²/min. or more. The ranges of the cardiac indices are given in Figure 8 in which prompt recovery is compared with early and delayed death. Central venous pressures of those who recovered were all within normal except at the outset, during the initial acute phase when dehydration and elevated hematocrits were present. In only two patients of this group was arterial hypotension present at any time. In none was uncompensated acidosis present after

Prolonged Recovery

Day 3–7						Week 2						Week 3						Time of Recovery
CI.	BP.	CVP.	pH	BB	Lact. Pyr.	CI.	BP.	CVP.	pH	BB	Lact. Pyr.	CI.	BP.	CVP.	pH	BB	Lact. Pyr.	
3.5	160/80	6	7.46	−2	20/3	3.6	155/82	5	7.44	+3	16/3	4.2	154/86	4	7.43	+3	14/2	7 wk.
7.0	120/60	5	7.48	+2	11/3							3.6	123/65	4	7.44	+3	12/3	2 mo.
3.4	110/70	14	7.45	−2	13/3	5.2	110/80	7	7.45	−3	34/6	3.9	112/60	7	7.45	+2	17/4	3 mo.
3.6	115/70	6	7.46	+2	18/3	3.9	125/70	7	7.43	+3	19/4	3.6	122/70	5	7.44	+3	15/3	1 mo.

treatment had been instituted, although transient severe metabolic acidosis (-12 mEq./L.) occurred in three. Arterial carbon dioxide tensions ranged as low as 30 mm. Hg, but the majority were normal. Lactacidemia of a modest extent (average 31 mg. %) was present after operation. In only two patients (#4 and #12) did the lactate-pyruvate ratio exceed 5. In two patients (#6 and #12) the arterial blood oxygen fell below 90% saturation; both were treated with respirators (see Fig. 3).

As an example of the extent to which dehydration and cardiovascular decompensation can progress, the course of Case 11 is presented in Figure 2.

This 11-year-old boy was admitted with a 36-hour history of small bowel obstruction. Central venous pressure was −2 cm. H_2O with a cardiac index of 1.5 L./M.^{2}/min. He was hypotensive. Body temperature had fallen to 35.6° C. He was severely acidotic: arterial pH 7.28 and buffer base deficit −15 μEq./L. Infusion of 1,500 cc. of isotonic saline restored central venous pressure to 7 cm. H_2O, accompanied by an increase of cardiac index to 3.6 L./M.^{2}/min. In part, the severe hemoconcentration (hematocrit 49%), hyperkalemia (5.3 mEq./L.), and hyponatremia (122 mEq./L.) were corrected. Following resection of a perforated gangrenous loop of ileum, cardiac output rose to 4.2 L./M.^{2}/

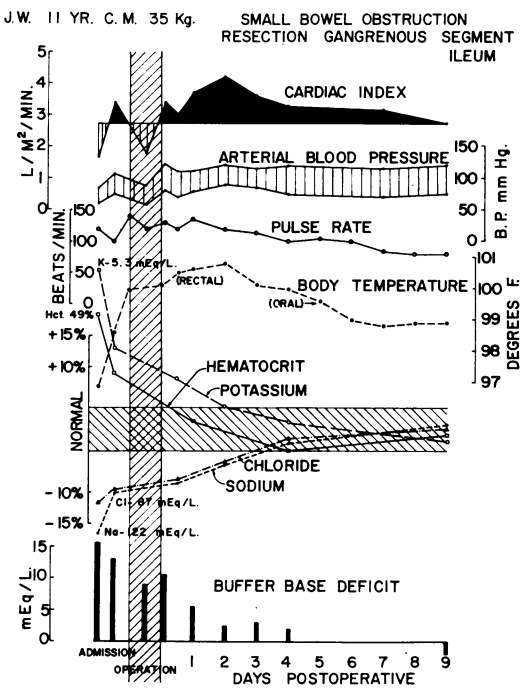

FIG. 2. The course of an 11-year-old boy admitted in a state of severe dehydration with peritonitis secondary to a perforated strangulated loop of ileum. Note response to rehydration and subsequent high cardiac output during the first four days. For details see text.

TABLE 3. *Hemodynamic, Respiratory and Metabolic*

Case No.	Diagnosis	Observation	Treatment	Hemodynamic C.I.	Pulse	B.P.	Mean B.P.	C.V.P.	Respiratory Body Temp.	Resp. Rate
Acute Deaths										
(17)	M. B. 74 CF	Preop.	Fluids & blood	3.4	138	88/60	(69)	12	100.8	20
	Ca. and ulcerative colitis. Perforation	Postop. laparotomy		2.0	140	60/42	(48)	16	101.0	25
(18)	L. F. 52 CF	Preop.	Fluid & blood	5.2	96	60/40	(47)	16	100.8	25
	Gangrene, bowel.	3 hrs. postop.		4.1	48		(38)	24	—	30
	Perforated.	6 hrs. postop.		1.2	24		(20)	14	101.4	28
(19)	B. P. 37 CM	Preop.	Fluids	4.7	140	110/86	(94)	0	102.6	26
	Gangrene, bowel.	2 hr. postop.	Blood	2.4	120	90/76	(81)	1	100.4	20
	Perforated.	24 hr. postop.		3.6	120	98/80	(86)	−1	99.2	28
		36 hr. postop.		1.4	110	75/50	(60)	5	97.0	32
(20)	R. C. 65 CM	1st. obs.; 1.8 L. NaCl soln.		2.1	138	122/90	(101)	7	101.0	50
	Bowel obstruction. Perforation.	3 hr. later; 1.3 L. Hartman		1.6	128	102/60	(73)	5	101.4	40
Delayed Deaths										
(21)	S. B. 29 WF	3 da. levophed		2.3	140		(70)	7	104.0	22
	Septic abortion.	3 da.		2.6	160	78/60	(66)	10	104.1	28
	Perforated uterus.	3 da. respirator		3.2	110		(82)	10	100.0	25
		5 da. respirator		1.5	90		(50)	22	96.2	30
		5 da. hemodyal		1.9	100		(86)	19	98.4	28
		6 da. respirator		1.4	104		(54)	22	97.2	26
(22)	A. McC. 41 WF	12 hr. postop.; ileostomy		2.3	130	80/60	(67)	5	102.0	28
	Ca. ovary.	1 da. postop.; 3.5 L. saline		4.2	124	116/70	(85)	2	99.4	28
	Gangrene, colon. Colon resection.	2 da. postop.; 3.4 L. saline		2.1	118	120/70	(87)	9	99.4	18
(23)	J. B. 58 CF	1 hr. postop. gastro-enterostomy		1.9	96	80/50	(60)	18	102.0	28
	Ca. pancreas.	21 hr. postop. respirator		2.3	117	100/70	(80)	19	101.4	22
	Metastases.	2 da. postop. respirator		4.1	108	150/90	(110)	17	103.0	22
	Wound infection.	2 da. off respirator		3.7	104	114/70	(85)	7	100.0	30
	Anastomosis leak.	6 da. respirator		2.9	116	180/110	(133)	14	99.4	22
	Wound dehiscence.	8 da. off respirator		1.8	102	120/74	(90)	6	99.4	30
		10 da. respirator		2.8	98	120/74	(90)	5	99.6	22
		12 da. respirator		1.8	116	104/80	(88)	5	98.8	22
Late Deaths										
(24)	L. W. 60 WM	Preop.		2.6	100	120/80	(93)	4	97.6	21
	Ca. hepatic duct.	Postop. 1 hr.		3.4	70	145/80	(102)	7	101.0	22
	Subphrenic abscess.	1 da.		3.4	100	80/50	(60)	3	99.8	26
	Subphrenic abscess.	3 da.		2.2	80	118/72	(87)	3	100.8	22
	Drainage. Spread.	6 da.		1.7	88	102/72	(82)	4	96.4	25
	Malnutrition.	7 da.		1.2	88	70/—	(35)	18	—	15
(25)	I. W. 51 CM	Preop.		3.3	120	140/90	(107)	0	101.0	28
	Obstruction.	Postop. 4 da.		3.8	104	180/110	(133)	4	101.6	32
	Gangrene, bowel.	20 da.		3.4	105	160/105	(124)	4	100.8	26
	Resection.	30 da.	Drainage	3.2	100	152/95	(114)	—	99.6	22
	Disruption.	40 da.		1.8	106	120/60	(80)	7	100.6	28
	Fistula.	41 da.		1.1	92	75/50	(62)	15	98.2	32

Values Accompanying Fatal Peritonitis

Metabolism										
Acid Base		Art. Blood Gas		Electrolytes						
Art. pH	ΔB.B.	pCO_2	O_2% Sat.	Na	K	Cl	Lact.	Pyr.	Hematocrit	Remarks
7.33	−5	36	93	137	2.8	116	—	6.3	36	Heart failure. *Died* 3 hrs. later.
7.21	−12	31	94	134	3.0	112	26	5.0	36	
7.20	−11	37	93	129	7.1	101	36	6.0	35	Anuria. Hyperkalemia. Heart
7.17	−19	23	92	127	7.2	101	72	6.3	34	failure. *Died* 30 min. later.
7.09	−19	32	93	128	7.7	102	70	6.1	34	
7.46	−2	26	96	124	4.7	103	11	2.2	26	Hyponatremia. Hyperkalemia.
7.47	0	34	93	129	4.5	106	16	2.7	—	Hypovolemia. *Died* 12 hr. later.
7.35	−3	39	91	125	6.2	99	13	3.4	—	
7.21	−4	39	92	121	—	—	20	3.6	32	
7.38	−5	31	98	141	3.8	120	28	3.3	40	Heart failure. Hypovolemia. *Died*
7.29	−8	30	94	140	4.0	117	26	3.4	41	1 hr. later.
7.27	−14	24	93	124	5.3	93	22	5.1	30	Hyponatremia. Anuria. Acidosis.
7.20	−17	25	92	127	5.4	94	16	7.8	28	BUN 257. Hyperkalemia. *Died*
7.29	−17	16	97	127	5.0	95	12	3.7	26	3 hr. later.
7.09	−21	30	95	134	7.0	94	14	5.4	28	
7.31	−9	30	93	134	5.2	93	12	5.0	34	
7.03	−17	46	93	134	7.7	91	21	5.0	30	
7.22	−15	28	93	144	6.5	118	30	7.2	26	? Hypovolemia. Heart failure.
7.38	−3	34	93	—	—	—	31	5.9	28	*Died. Gastrointestinal bleeding*
7.36	−5.7	32	93	144	5.5	107	21	5.4	30	10 days.
7.48	1	33	88	125	2.1	87	52	9	35	Dehydration. Hyponatremia.
7.53	4	39	98	128	2.4	92	52	10	37	
7.48	6	35	97	138	2.8	99	47	7	30	
7.51	8	38	84	147	2.7	104	23	5	34	
7.43	2	30	97	157	4.3	118	12	2.5	—	Pneumonitis.
7.34	2	42	86	152	3.9	113	12	3.1	32	
7.42	−3	29	93	148	4.5	114	24	4.5	—	
7.34	−11	22	93	132	6.1	110	56	7.7	25	Hyperkalemia. *Died* 1 day later.
7.45	3	39	93	135	4.6	103	11	3	37	Weight loss—103 to 78 lbs. Heart
7.41	3	41	92	141	5.5	107	35	5	43	failure. *Died* 40 min. later.
7.49	4	33	93	135	3.2	104	10	3	—	
7.35	−2	40	93	129	2.2	102	—	—	39	
7.47	2	30	91	126	4.3	102	16	6	40	
7.36	−2	38	90	135	3.9	104	21	5	42	
7.44	=1	31	96	133	4.5	104	41	4.2	28	Weight loss—162 to 129 lbs.
7.46	+1	32	96	133	4.2	100	19	3.7	32	Pneumonitis. Heart failure—
7.44	+3	36	94	135	3.8	102	16	3.2	34	oliguria. *Died* 1 day later.
7.45	+3	36	93	132	3.4	101	18	4.1	34	
7.43	−3	35	90	130	4.2	100	16	5.1	33	
7.34	−5	32	88	128	4.4	96	25	5.0	34	

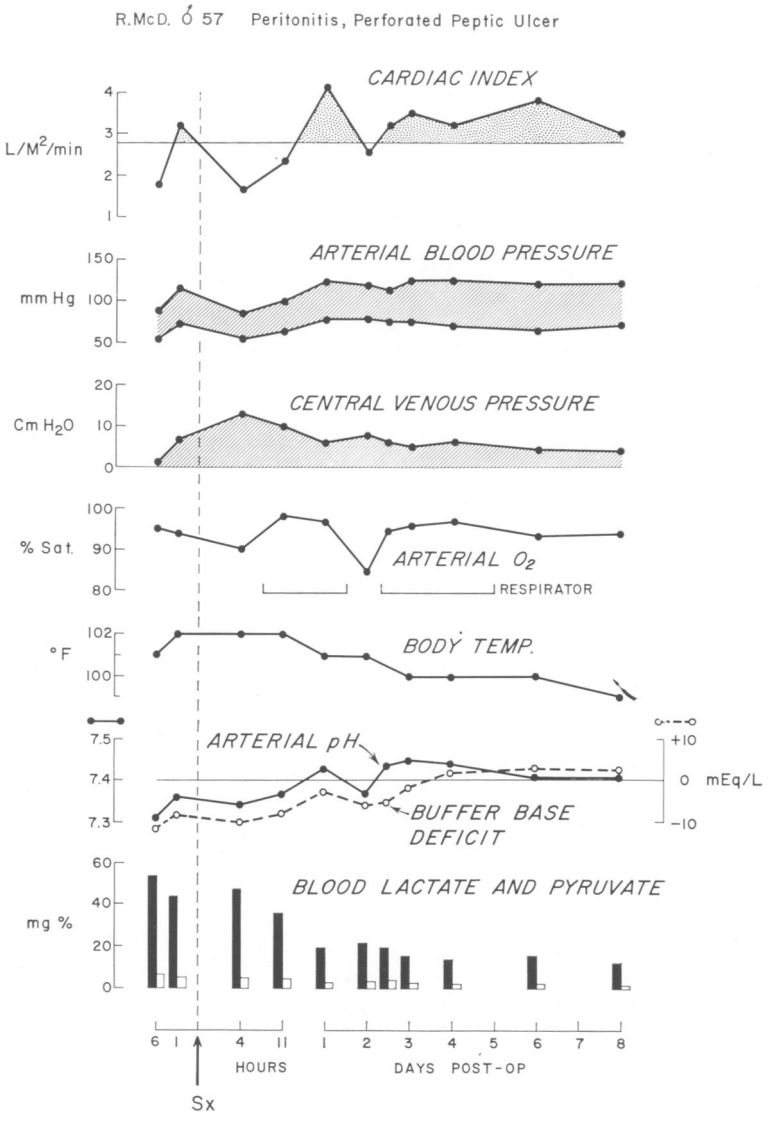

FIG. 3. The course of a 57-year-old man admitted with a perforated ulcer of at least 11 hours' duration which resulted in generalized peritonitis. Course was complicated by respiratory failure which was corrected by the use of mechanical ventilation by a respirator. For details refer to text.

min., with a temperature of 38.1° C. This lasted 2 more days, followed by a gradual return toward normal as he went on to make an uneventful recovery. As soon as the cardiac output rose above the normal resting value, the urinary output which had been absent on entry was resumed. The blood urea nitrogen decreased from 41 to 26 mg.% in the first two days. The 24-hour cortisol excretion was 30 mg. on the first day, returning to a value near 15 mg. within three days.

Case 12 is presented in Figure 3 to illustrate how a respirator was employed to improve the metabolic and circulatory condition of a patient who was suffering from inadequate pulmonary gas exchange and increased work of respiration.

This 57-year-old man was admitted with a perforated ulcer, judged to be of 11 hours' duration. Rehydration restored his central venous pressure from 2 to 6 cm. H_2O with a rise of cardiac index from 1.8 to 3.2 L./M.²/min. He too exhibited a severe metabolic acidosis (−12 mEq./L.), accompanied by lactacidemia of 57 mg.%. At operation a perforated duodenal ulcer was closed. About 2 liters of foul material were sucked from the peritoneum. Postoperatively his course was

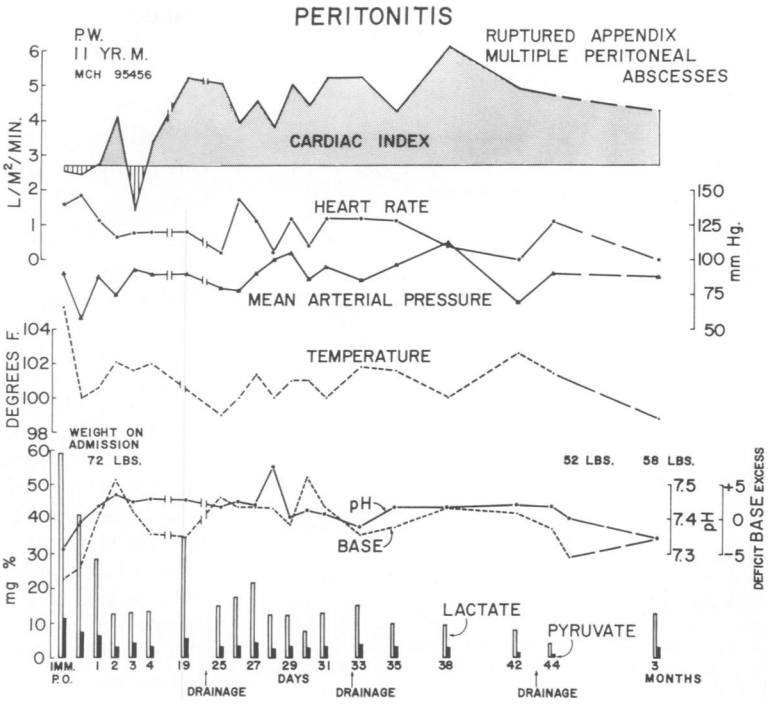

FIG. 4. The course of an 11-year-old boy who made a "Late Recovery." He was admitted with a perforated appendicitis and generalized peritonitis. Numerous secondary abscesses and colonic fistulas delayed his recovery. Note prolonged high cardiac output associated with fever and great weight loss. For details refer to text.

complicated by pneumonitis which responded to chemotherapy and the use of a respirator for several days. However, his metabolic imbalance was corrected, and his cardiac index ranged from 3.2 to 4.1 L./M²/min. throughout the first week. Thereafter, convalescence was uneventful.

Prolonged Recovery. Four patients whose data are summarized in Table 2 continued to have infections which required multiple drainage procedures for isolated abscesses or the closure of intestinal fistulae. Only one of these was not suffering from deranged circulatory dynamics and metabolism at the onset.

Case 14 had localized spontaneously both a liver and a subhepatic abscess secondary to rupture of the liver sustained in an automobile accident 6 weeks before. At operation, however, the need for control of severe bleeding caused considerable contamination of the peritoneum. Like others with continued infection, isolated eventually by inflammatory reactions, he continued to maintain high cardiac outputs until such time as the infection was eliminated. Instead of subsiding toward normal resting value at the end of the first week as occurred in those with uncomplicated recovery, cardiac indices in the third week ranged from 3.6 to 4.2 L./M.²/min. This was accompanied in most instances by daily fever up to 38.9° C. With the exception of a moderate degree of alkylosis and tachypnea, the metabolic status remained normal. Urinary function after the initial insult was adequate in all four. Weight loss ranged from 21 to 30 per cent of the best weight prior to the illness, in three of the four patients.

The only patient to maintain his weight was Case 18. Case 15 is another example of the pattern of prolonged recovery (Fig. 4). At operation upon this 11-year-old boy, an acute ruptured appendicitis with generalized peritonitis was discovered. During closure of the abdominal wound, cardiac arrest occurred from which he was promptly resuscitated by closed cardiac massage. Immediately after operation, he was found to be in a very severe state of lactacidemia (59 mg.%) and metabolic acidosis (−9 mEq./L.). The cardiac index was 2.5 L./M.²/min. Following further rehyration with isotonic saline solution, 1.1 L., his acidosis was corrected as the cardiac index rose to 4.1 L./M.²/min. Thereafter, his metabolic status remained quite normal except for a loss of weight from 72 to 52 pounds, this despite an average daily intake approaching 3,000 calories. In part, malnutrition was due to a cecal fistula and subsequently a colonic fistula of the splenic flexure, both

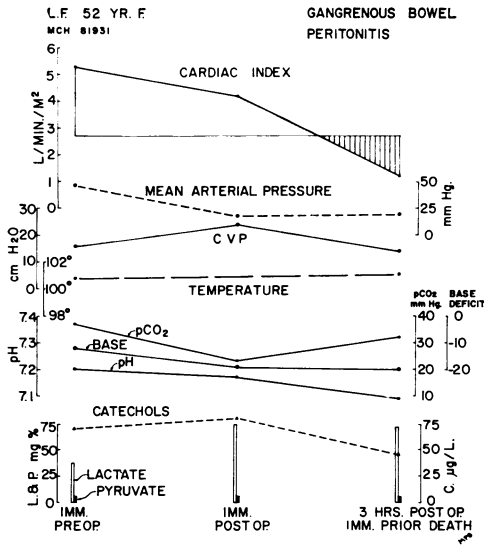

FIG. 5. The course of a 52-year-old woman who died shortly after a hemicolectomy for a gangrenous right colon. This is an example of an "Acute Death," probably the result of overwhelming infection and the presence of bacterial endotoxin. For details refer to text.

of which healed spontaneously. Throughout this period the cardiac index ranged from 3.9 to 6.2 L./M.²/min., falling each time an incison and drainage effectively released pus from an abscess.

Acute Deaths. Examination of data in Table 3 indicates that the initial high cardiac outputs of Cases 17, 18 and 19 could not be maintained. Within a relatively few hours the cardiac indices had fallen to values ranging from 1.2 to 2.0 L./M.²/min. As suggested by high terminal central venous pressures (7, 14 and 16 cm. H_2O), three of the four patients in this group died in heart failure. Each had positive blood cultures, two with coliform bacilli and one with gram positive cocci. Case 18, whose course is illustrated in Figure 5, was the only one who proved incapable of maintaining the arterial blood pressure at or near normal by an increase of the total peripheral vascular resistance. She remained profoundly acidotic with an arterial pH down to 7.09 and lactic acid elevated to 70 mg.%. Like Case 19 she was anuric and had developed a severe hyperkalemia (K = 7.7 mEq./L.) prior to death.

Delayed Deaths. Three patients, who started to recover in the normal fashion, subsequently developed complications interfering with their capability of maintaining the high cardiac indices. This comparison is shown in Figure 8. Case 21 was one of the two patients not operated upon.

She was a 29-year-old woman who proved at autopsy to have a perforated uterus. She started to improve by the third day, at which time she had a cardiac index of 3.2 L./M.²/min., but at the same time she was severely acidotic (arterial pH 7.29 and buffer base deficit of −17 mEq./L.). It is of interest that each time she was given norepinephrine her cardiac output decreased despite an elevation of arterial blood pressure. She was continuously oliguric and became anuric on the third day. As hyperkalemia progressed to 7.0 mEq./L. on the fifth day with a blood urea nitrogen of 257 mg.%, it was apparent that she was in heart failure. The cardiac index was 1.5 L./M.²/min., associated with a central venous pressure of 22 cm. H_2O. Hemodialysis reduced the blood potassium to 5.2 mEq./L. with a transient rise of the cardiac index to 1.9 L./M.²/min. Inexorably, the process continued. She died on the sixth day in heart failure with a plasma potassium concentration of 7.7 mEq./L.

Case 22, the second of the patients whose death was delayed, appeared slightly cyanotic in the nail beds and lips on the second day following a right hemicolectomy for gangrene and perforation. Her arterial blood oxygen was 93 per cent saturated. Despite a normal blood pressure she had a cardiac index of 2.1 L./M.²/min. Central venous pressure which had risen from 5 to 9 cm. H_2O suggested the possibility of heart failure. However, she did not respond to digitalis. This was accompanied by a moderate metabolic acidosis (buffer base deficit: −6 mEq./L.). Unfortunately, no further hemodynamic measurements were made upon this patient, but she continued to give evidence of the "low output syndrome." On the tenth day she exsanguinated from gastrointestinal hemorrhage.

The course of the third patient in this group, Case 23, is presented in Figure 6.

A 58-year-old woman was explored because of a mass in the epigastrium and duodenal obstruction. At operation a carcinoma of the pancreas

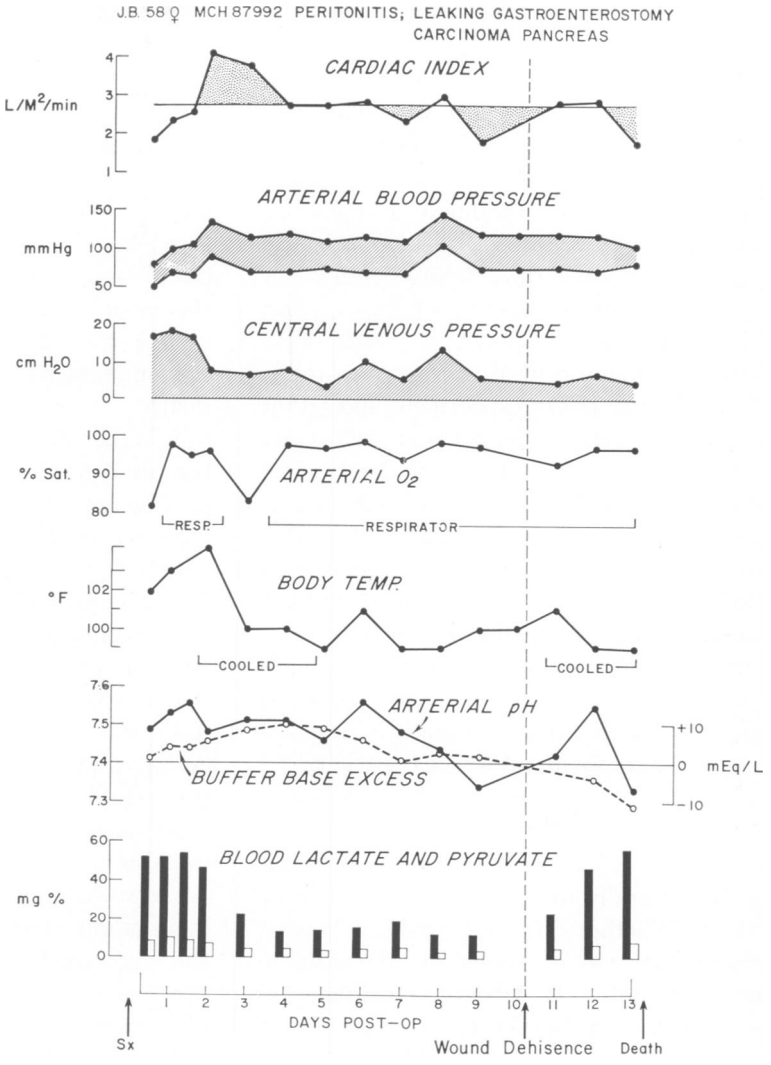

FIG. 6. The course of a 58-year-old woman who developed peritonitis and a wound dehiscence secondary to a leaking gastroenterostomy. This is an example of a "Delayed Death" in which the patient was unable to maintain cardiac output sufficient to meet demands for circulation adequate for metabolic requirements.

was discovered. Gastroenterostomy was performed. Postoperatively she was in shock for unknown reasons, probably related to heart failure, with a venous pressure of 18 cm. H_2O and a cardiac index of 1.9 L./M.²/min. Because of the low output and arterial oxygen desaturation of 88 per cent she was connected to a mechanical respirator. She appeared to be making a good recovery despite development of metabolic alkalosis (buffer base excess +8 mEq./L.), perhaps related to gastric suction. Cardiac index rose to 4.1 L./M.²/min. Shortly thereafter body temperature reached 39.4° C. Pneumonitis was evident on the eighth day. Her cardiac index fell to 1.8 L./M.²/min. Oliguria followed and blood urea nitrogen was 127 and blood potassium 6.1 mEq./L. on the twelfth day. With a cardiac index of 1.8 L./M.²/min., she became progressively more acidotic (buffer base deficit −11 mEq./L.). In the meantime she had developed a fistula from a leaking anastomosis and subsequently a wound dehiscence on the eighth day. A blood culture on the tenth day was positive for Enterococci. It was possible to maintain her blood pressure by an infusion of norepinephrine, with a moderate elevation of the cardiac output. It is of interest that at the time of her initial episode of shock, following the exploration and gastroenterostomy, she had a 24-hour urine excretion of cortisol of 28 mg. This fell to 14 and subsequently to 12 mg. prior to the onset of oliguria on the tenth day.

Late Deaths. Two patients (Cases 24 and 25) died after prolonged peritoneal infection. Both suffered extreme emaciation secondary to failure of gastrointestinal function. Their body weights declined from 103 to 78 pounds and from 162 to 129 pounds, respectively. Each continued to maintain adequate cardiac indices of 3.4 L./M.^{2}/min. or more until a few days before death when it declined. Not until outputs fell to 1.2 and 1.1 L./M.^{2}/min., respectively, with rapid elevations of the central venous pressure to 18 and 15 cm. H_2O, respectively, did either become acidotic. Neither was there any evidence of oliguria or hyperkalemia. The course of Case 24 is presented in Figure 7. He had extensive subphrenic and subhepatic abscesses secondary to carcinoma of the bile ducts. These were drained without benefit. At autopsy multiple abscesses were found in other areas of the peritoneum. Presumably these were the result of what may have been a bile peritonitis which had occurred acutely about 6 weeks earlier.

Discussion

Local metabolic requirements are conceded generally to control the perfusion of tissues. Whether due to hypoxia or lack of other substrates, accumulation of metabolic products causes the arterioles to dilate.[6, 21] In turn, the cardiac output is adjusted to satisfy the demands for circulation by reflexes initiated from the basoreceptors and chemoreceptors, mediated through the venomotor system.[4] Through stimulation of the cardiac accelerator nerves, the heart is made to beat faster and often at a smaller end diastolic volume.[36] Only when cardiac output proves incapable of maintaining adequate perfusion of all tissues is arterial blood pressure guarded by an increase of total peripheral vascular resistance. This is effected through sympathetic nerve stimulation and the secretion of catechol amines at the end organs and the adrenal medulla.

The areas initially denied a portion of their required circulation are the skin, splanchnic bed, kidneys and nonworking muscles. Here anaerobic glycolysis occurs, accompanied by a progressive increase of lactic acid and other acid metabolites. This has been referred to as "hypoxic acidosis." Compensatory respiratory alkalosis requires an increase of respiratory effort. This in turn places an additional demand upon the circulation, already inadequate, to perfuse the muscles of respiration.[8, 24] If not corrected, the situation leads to progressive uncompensated acidosis and ultimately death.

Whether the inadequacy of circulation is the result of abnormally low cardiac output or a demand for blood flow in excess of the capacity of the cardiovascular system to supply it, a metabolic state of shock exists.[7] The data presented indicate that in patients with peritonitis, one or both situations existed at various phases of the illness. At the outset while peritonitis was developing, a low cardiac output was frequently present. As the illness progressed and inflammation was established, a greater than normal cardiac output was required to satisfy the metabolic needs of the body. Data in Table 3 show that as long as peritonitis and inflammation continued, failure to maintain the high cardiac outputs resulted in progressive metabolic derangements from lack of transport.

In the early phase of developing peritonitis, two causes for inadequate circulation may be present. The first is the hypovolemia accompanying the formation of a large third space, and the second is the loss of venous return and myocardial failure associated with the presence of bacterial toxins.[18, 39] Part of the inflammatory reaction is a local increase of capillary permeability with the escape of water and other blood elements from the vascular system.[28] Cope *et al.*[10] described the voluminous protein-containing peritoneal fluid of peritonitis and the similarity of this to extensive surface burns. Fluid is translocated into the tissues, the lumen of the gut and the peri-

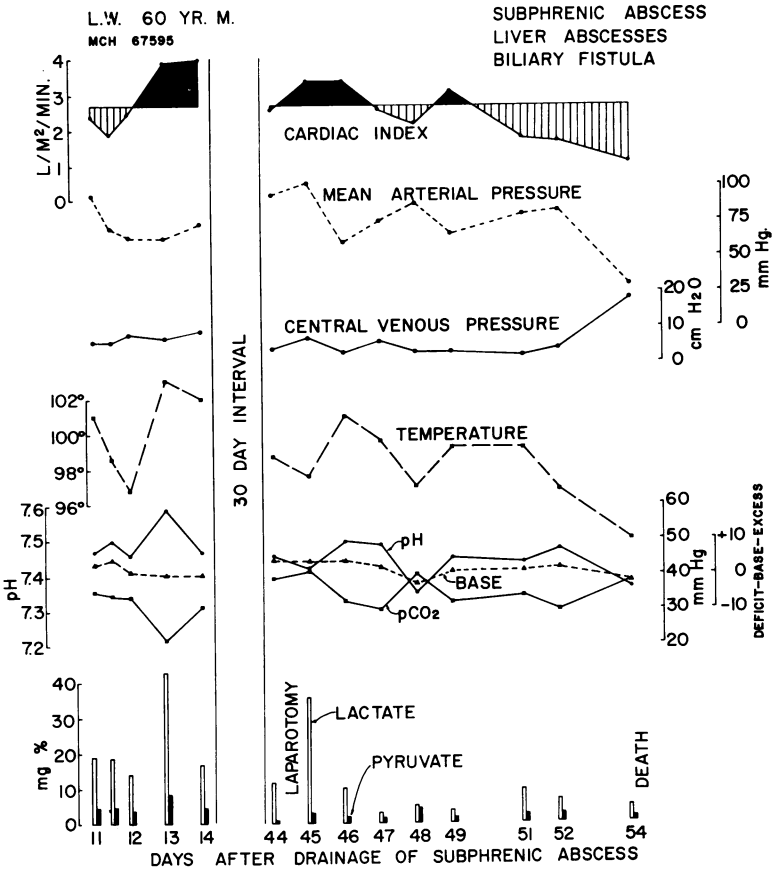

FIG. 7. The course of a 60-year-old man, an example of a "Late Death," who had a prolonged course of peritonitis following drainage of liver and right upper quadrant abscesses secondary to carcinoma of the bile ducts. During the course his weight decreased from 103 to 78 lbs. Ultimately he proved unable to maintain an adequate cardiac output and died in heart failure. For details refer to text and Table 3.

toneal cavity. The extent to which formation of a huge third space can progress is illustrated by Cases 11, 12, 13, 14 and 16, as well as 19. The latter patient died.

As hypovolemia and circulatory insufficiency develop, a decrease of tissue oxygen tension results in failure of the "sodium pump." Potassium is released from the intracellular space.[14] Lack of urinary excretion inevitably is followed by hyperkalemia. Retention of the water of oxidation dilutes the available sodium as the extracellular space expands.[30] The combination of hyperkalemia and hyponatremia, shown in Figure 2, further contributes to myocardial failure and to other tissue dysfunction. This situation was found to exist in three of the patients who died acutely (Table 3).

Improvement of the circulatory and metabolic state effected by the intravenous infusion of isotonic sodium chloride solution in the majority of these patients shows the need to restore a normal circulating fluid volume. As the central venous pressure increased to 4 cm. H_2O or more, cardiac output usually rose above the normal resting value of 2.8 L./M.^{2}/min. When guided by measurements of the central venous pressure to avoid pulmonary congestion, saline can be administered rapidly. As much as 50 cc./Kg. body weight were required in the first 12 hours. As the plasma sodium concentration increased, that of potassium decreased, when urine production was re-established. Under these conditions of dehydration, when abnormally high hematocrits are present, the infusion of whole blood is not indicated. Excessive use of sodium chloride must be avoided in the absence of urine production to prevent hy-

perchloremic acidosis, as was observed in Cases 20, 22 and 23. Under these conditions sodium bicarbonate could better be employed to avoid excessive anion accumulation. A case could be made for the use of plasma to replace the protein colloid lost into the inflammatory area.[10] In addition to its effect in restoring electrolyte values sodium chloride solution prevents to some extent the adverse effects of hemagglutination. In this respect dextran might be of more value, as well as for its colloid effects.[26]

Yet a number of patients failed to respond to restoration of fluid volume. The presence of bacteremia in three who died early and two who died subsequently (Cases 17, 18, 20, 21 and 23) suggests that they were subject to septic shock. At least the presence of bacterial endotoxin contributed to heart failure and a low cardiac output. Renal failure, cited by Welch[42] as a common cause of death in peritonitis, appears to be related to a combination of low cardiac output, intense vasoconstriction and the presence of circulating toxins, pigments and other products of necrotic tissue.[35] Since available information on septic shock recently has been well summarized,[29] an extensive discussion of this topic will not be undertaken. Suffice it to state that unless the septic focus can be brought under control by resection, drainage or occasionally by massive doses of antibiotic agents,[40] recovery seldom occurs. Examples of this are Cases 3, 4, 8, 12 and 13. Case 4 was particularly dramatic in this regard. Following resection of a perforated infected uterus, the result of a septic abortion, the cardiac index rose and the patient's metabolic state improved. If the source of the circulating endotoxin, a lipopolysaccharide, is not eliminated in peritonitis, supportive measures including administration of large doses of cortisol[39] usually fail. It has been suggested that cortisone may stabilize the lysosomal membrane[23, 41] as well as serve as a vasodilator.[27] Such was the situation in Cases 20 and 21. Occasionally, small doses of norepenephrine have been found to increase slightly the cardiac output (Case 23, Fig. 6), but generally there is only a rise of blood pressure accompanied by a worsening of the metabolic situation. Every time a vasoconstrictor drug was administered to Case 21, the cardiac output declined. Vasodilator drugs have been recommended and found to be effective in improving the metabolic state under certain circumstances.[29] No experience with this form of therapy was obtained in this series.

It appears that in an infection as extensive as diffuse peritonitis, effective measures are those which allow the normal processes of inflammation to wall off the infectious process. Peritonitis is frequently a self-limiting disease if the contaminating source is removed.[13, 42]

Data in Figures 1 through 4, and those in Tables 1 and 2, indicate that as soon as the cardiovascular system is capable of responding, it is required to satisfy an abnormally large demand for circulation. This is the second phase of recovery. Should the extra cardiac output not be forthcoming at this stage for any reason, metabolic deterioration and death follow. This is illustrated by the patients whose death was "delayed" or "late" (Table 2). Examples are given in Figures 6 and 7. Comparison of the circulatory state of those who died and those who survived (Fig. 8) further emphasizes this point.

The reasons for the high cardiac indices, once such an extensive inflammatory process is established, are several. Fever itself raises the rate of chemical reactions and the metabolic rate.[25] Hopkirk *et al.*[20] reported elevation of the metabolic rate in patients during the acute phase of peritonitis. Heat loss and evaporation are effected by augmented circulation to the skin. As oxygen requirements increase or when the arterial pCO_2 must be reduced to compensate for metabolic acidosis under these conditions, respiratory effort must be in-

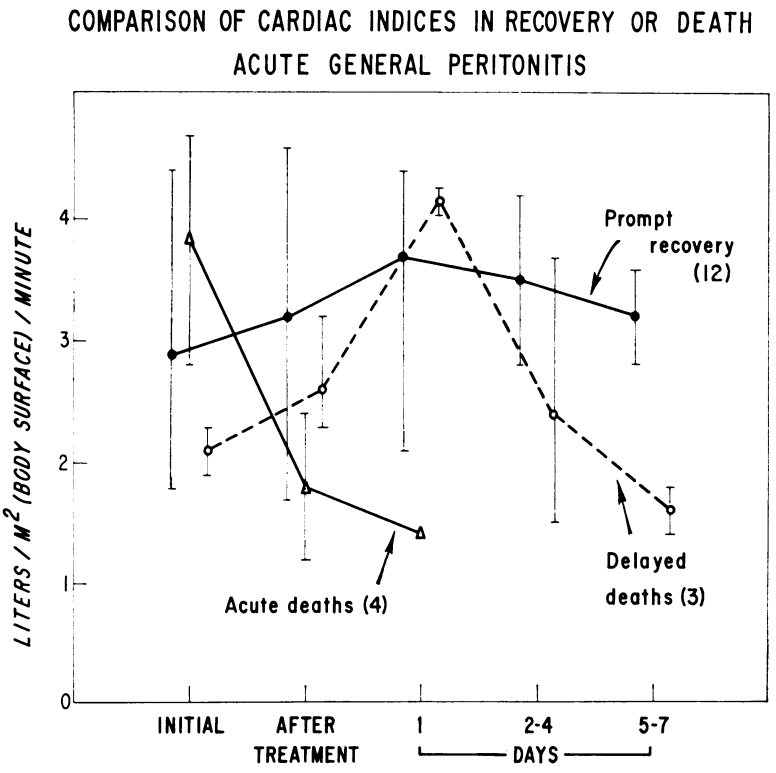

FIG. 8. Comparison of circulatory responses of patients who made "Prompt Recovery" with those who died acutely and those with "Delayed Deaths." Note high cardiac indices of those who recovered in comparison with patients who died. Vertical bars represent ranges of observations.

creased.[31] This requires greater perfusion of the respiratory muscles.[8] Recent work by Albrecht and Clowes[1] suggest that an inflammatory area serves to some extent in the fashion of an arteriovenous shunt. As may be seen in Figure 4 a reduction in the extent of the inflamed tissue by the drainage of isolated abscesses frequently is accompanied by a decrease of fever and cardiac output.

A large caloric energy expenditure is involved in maintaining cardiac output, respiratory activity and other functions in peritonitis. Moore[32] and others[25, 42] state that malnutrition caused by failure of gastrointestinal functions can lead to dissolution of the organism. This is illustrated in the prolonged course of the case illustrated in Figure 7. It appears that as sources of energy, stored fat and protein were exhausted, metabolism and heat production failed. On the fifty-first day of the disease, when body weight had decreased to 78 pounds, body temperature began to fall. Only terminally was there evidence of heart failure, indicated by an elevation of central venous pressure. The four patients who survived prolonged illnesses (Table 2) gave further evidence of the need for a high cardiac output to continue the massive caloric energy expenditure[31] associated with extensive unresolved infection. The 11-year-old boy (Fig. 4) lost 20 pounds in 44 days despite an average intake approximating 3,000 calories per day. Throughout this time, cardiac index ranged from 4 to 6 L./M.^{2}/min. These data add emphasis to the oft-quoted maxim that nutritional intake is dependent primarily upon gastrointestinal activity. Only by its maintenance can the metabolic substrates for excess caloric expenditure be satisfied in a prolonged inflammatory illness.

Burke and Welch,[5] Swenson[38] and Norlander *et al.*[34] described the respiratory failure associated with peritonitis. This may be the result of pneumonitis or interference with normal respiratory mechanics due to

bowel distention, or be due to exhaustion. Under these conditions, benefits of an efficient ventilator capable of assuming the work of respiration become apparent when one realizes that the "cost of respiration" is reduced at the same time as the oxygen saturation of the blood is improved. Clowes *et al.*[8] demonstrated by clinical observations that the cardiac output may fall as a respirator relieves the circulatory system of the need for perfusing the laboring muscles of respiration. Similarly, the metabolic situation may be improved in the presence of an inadequate cardiac output when the work of respiration is removed. Blood going to the respiratory muscles can then be diverted to other tissues for their metabolic improvement. Therefore, the use of respirator connected to a cuffed tracheostomy tube should be considered seriously in the presence of cardiac failure or shock syndrome early in the development of peritonitis. This form of therapy also may be of material benefit in the later phases of peritonitis. Both situations are illustrated by the patient whose data are presented in Figure 3.

From these data it is clear that the elevated metabolic activity and expenditure of caloric energy by many organ systems, in the presence of extensive peritonitis, requires the continued maintenance of abnormally high cardiac outputs to furnish the essential transport. This is in marked contrast to the circulatory requirements of an uneventful convalescence from a major operation which constitute little more than those of lying quietly in bed.[7] Is it any wonder that elderly patients or others with defective cardiovascular systems may survive an uneventful convalescence from a laparotomy in which an extensive procedure is carried out? Yet when extensive infection occurs, they die. This further confirms Moore's [32] statement that infection and inflammation loom large among the stimuli which excite the mechanisms of defence.

These observations point out not only the circulatory demands but also the metabolic and blood volume defects which may impede the heart and blood vessels from fulfilling their part in the body's defence. There is little doubt that any circulatory deficiency caused by this condition influences endocrine, respiratory and other responses which permit cellular metabolism to continue under adverse chemical conditions.

Summary

Serial hemodynamic and metabolic observations were made on 25 patients with diffuse fulminating peritonitis secondary to a ruptured viscus. Nine patients died.

Initially, as edema and peritoneal fluid were developing, hypovolemia and electrolyte derangements frequently resulted in cardiac indices well below the normal resting value of 2.8 L./M.^{2}/min. This was accompanied by metabolic acidosis and lactacidemia. The presence of bacteremia contributed further to inadequate venous return, apparent heart failure and low outputs during this early phase in three patients who died.

As soon as the cardiovascular system was capable of responding, elevated cardiac indices, ranging from 3.0 to 6.0 L./M.^{2}/min., were observed. If for any reason the sustained high cardiac output was not maintained as long as inflammation persisted, metabolic acidosis and death supervened.

The elevated metabolic rate and great caloric expenditure and the increased respiratory effort, as well as the local circulatory effects of extensive inflammation in peritonitis, are closely related to the increased requirements for circulation.

The rationale is discussed of therapeutic measures not only for support of the circulation, but also for reducing the circulatory requirements, related as they are to the metabolic demands of tissues throughout the body. These measures include surgical and chemotherapeutic steps to permit in-

flammatory isolation and control of the infection. The generous but controlled use of fluid and electrolytes, the respirator, reduction of elevated body temperature, and maintenance of nutrition all can contribute to the ability of the circulation to satisfy the transport needs throughout the body.

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Discussion

Dr. Watts R. Webb (Dallas): I would like to commend Dr. Clowes on these very elaborate studies beautifully presented here this morning. No one who has not had the opportunity, or the obligation of attempting to do extensive metabolic studies of this nature can really understand the vast amount of work that is involved, because every single point on each one of these slides represents almost a day's work for somebody; and it is so distressing at times to have an excellent study going, and something happens with one's losing much of the data at a very critical point.

The fact that he has been able to carry out so many studies in such fine style is certainly a tribute to his organizational abilities and to his forethought in managing this type of study. Certainly we wish to agree with the principles that Dr. Clowes has elaborated here. There are two or three things I would like to emphasize in addition.

The peritoneal surface itself represents almost the same surface area as the skin, and peritonitis in general can be compared to a very extensive burn. The fluid requirements, the electrolyte loss, the plasma loss in these can be compared to that in a very extensive burn, and acutely they are going to need extensive fluid replacement in very much the same fashion.

In fact, I think this may lead to one of the problems Dr. Clowes has outlined in the low cardiac output syndrome, which we believe often develops as a result of a persistent low blood volume. We have seen this very frequently, and when one can measure the spaces, one finds there is a persistent low blood volume. The patients develop excessive, perhaps inappropriate, vasoconstriction, as we like to call it, with a drop in the cardiac output. Frequently this can be reversed by infusion of large amounts of electrolyte solution or blood, whatever might be needed. Volume replacement of course, can be controlled and monitored by the central venous pressure, so that one does not throw these precarious patients into pulmonary edema.

We certainly agree with the concept of reducing the work of these patients as much as one possibly can, particularly with the use of the hypothermic blanket and the respirator.

Two years ago we would have said unhesitatingly to use the respirator. In the more recent months we have been seeing so many complications from the respirator and from tracheostomies that we have become very much more selective in their use.

The complications have been primarily from the gram negative pneumonias, and especially Pseudomonas. As you may remember, a few years ago Pseudomonas was regarded almost as just a contaminant, a nonpathogen, an organism that produced *laudable pus*. Today we all know that this is not true, and even with the use of 0.25% acetic acid nebulization throughout our unit at least three times a day, we still see some of these complications. While we like to use the respirator, we are very cautious in its application, and we realize that there is a certain price paid for its use.

Dr. Edward F. Parker (Charleston, S. C.): I too, would like to join Dr. Webb in congratulating Dr. Clowes on his organizational ability and his forethought in planning and executing these studies, which have done so much in elucidating the low cardiac output syndrome and the other metabolic and circulatory problems connected with the most serious illnesses encountered in the practice of medicine.