Original Articles

Hemodynamics and Blood Volume During Operation with Ether Anesthesia and Unreplaced Blood Loss

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THE CLASSIC approach to the management of the anesthetized patient who loses blood relies considerably on visual estimates of the magnitude of blood loss and clinical estimates of the adequacy of hemodynamics. Suggested aids to making decisions in this situation include serial measurement of the quantity of blood lost,[1] the peripheral hematocrit,[2] the venous pressure,[3] and the blood volume.[4] Advocacy of each particular approach has been based largely on personal experience with a single approach or on deduction from observations on animals. Discussion frequently is unrewarding because of difficulties posed by limited knowledge of the relationship, in anesthetized man, between blood volume and hemodynamics and the degree to which replacement of plasma volume occurs in response to unreplaced blood loss. This study is an attempt to bridge this gap by observing hemodynamics, blood volume, hematocrit, and amount of blood lost during unreplaced blood loss and ether anesthesia in man.

Material and Methods

Ten adults, 29 to 65 years old, without known serious medical disorders, were studied during operations, in the supine position, for unilateral (cases 1, 2, and 7) or bilateral varicose veins.[5, 6] All patients received pentobarbital (100 mg.) at 2 hours and meperidine (50 to 100 mg.) and atropine (0.4 mg.) at 1 hour before induction of anesthesia with thiopental (100 to 300 mg.) and intubation with the aid of succinylcholine (40 to 60 mg.). Anesthesia was maintained with a 6-liter per minute flow of nitrous oxide (65 per cent) and oxygen (35 per cent) and additional ethyl ether sufficient to maintain unconsciousness and lack of movement. Ether concentration in the inspired air was 2 to 3 per cent, and EEG levels were between I and II. Manual hyperventilation (mean airway pressure, 3 to 4 mm. of mercury) was used with a semiclosed-circle carbon dioxide absorption system. All patients were awake and responding after operation (3 to 9 hours in duration) and left the hospital without serious postoperative complications. Esophageal temperature averaged 36° C. and did not change more than 1° C. Variable amounts of intravenous (5 per cent glucose in 0.2 per cent NaCl) and flush (Ringer's) solutions were given. One patient (case 10) received 535 ml. of cross-matched blood at the end of operation. Transfusion therapy was not carried out in any other patient. Additional drugs were not given.

Cardiac output (dye-dilution method)* and pressures (airway, peripheral and central venous, and arterial) were measured hourly as previously described.[7, 8] Duplicate determinations did not differ by more than 10 per cent. Plasma volume (PV), cell volume (CV), blood volume (BV), peripheral hematocrit (H_c), body hematocrit (H_m), and the ratio of body to peripheral hematocrit (H_m/H_c) were measured before anesthesia (initial) and at the end of operation (final) as previously described.[9] Calculated blood loss was obtained by dividing the observed change in CV by the average of initial and final H_c. Samples of blood were taken approximately 15, 20, and 25 minutes after injection of I^{131}-

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* Indocyanine green (Cardiogreen) supplied for these studies by Hynson, Westcott and Dunning, Baltimore, Maryland.

labeled serum albumin (RISA) and 20, 25, and 30 minutes after injection of Cr^{51}-tagged erythrocytes. For 18 of the 20 observations, the slope of the line used to extrapolate RISA concentrations back to zero time averaged −8 per cent per hour with a range of −3 to −14 per cent. These agree well with the 4 to 10 per cent apparent loss observed during the first hour after injection of T-1824 in man.[10] In the final determinations in cases 1 and 3, slopes were −23 and −33 per cent per hour, respectively. These aberrant observations were associated with inadvertent rapid administration of intravenous fluids and were discarded as not appropriate to the calculation of plasma volume. Final values for PV and BV in these two instances were calculated from final values for CV and H_c and initial value for H_m/H_c on the assumption that little change had occurred in the H_m/H_c ratio. This seems justified by the similarity of individual initial and final values for H_m/H_c in the eight other cases (table 1). Cell volumes were calculated from the average of the concentrations of cell indicator observed at 25 and 30 minutes. In individual patients these consecutive concentrations agreed within 1 per cent in 14 of the 20 observations and within 2 per cent in all. The value for Cr^{51} "tag concentration" used in the initial determination of CV agreed within 1 per cent of that observed in the background sample drawn prior to the final determination of CV in all but cases 5 and 7 (3 per cent) and case 10 (received blood by transfusion).

Surgical blood loss was estimated by a modification of the electrical conductivity method [1] in which a washing machine and 20 to 40 liters of distilled water were used for extracting blood from sponges and linen, and individual calibration curves were constructed with aliquots of the water and the patient's blood. Recovered loss refers to the sum of surgical and sampling losses. In six consecutive patients, the mean difference between calculated (blood volume methods) and recovered (surgical plus sampling) blood loss was 2 per cent with a total range of −4 to +7 per cent. Arterial *p*H and P_{CO_2} were determined by *p*H and P_{CO_2} electrodes maintained at 37° C. and calibrated with appropriate buffers and analyzed gases, respectively.

A needle was placed in the left antecubital vein for injection of RISA, Cr^{51}-tagged erythrocytes, and fluids, and for measurement of peripheral venous pressure. A catheter (Intramedic PE-90), passed centrally via the right antecubital vein to a site where central pressure contours and dye curves characteristic of a central injection were obtained, was used for measurement of central venous pressure, for injection of dye, and for blood sampling.

TABLE 1. Blood Volumes and Hematocrits Before (Initial) and After (Final) Operation

Case	Blood Volumes								Hematocrits			
	Initial				Initial–Final			Change in BV as % of Initial	Initial		Final	
	PV (ml.)	CV (ml.)	BV (ml.)	BV (ml./kg.)	PV (ml.)	CV (ml.)	BV (ml.)		H_c	H_m/H_c	H_c	H_m/H_c
1	2648	1619	4267	63	145*	199	344*	8	0.424	0.89	0.405	—
2	2847	2150	4997	71	202	393	595	12	0.473	0.91	0.445	0.90
3	2892	1798	4690	52	253*	339	592*	13	0.417	0.92	0.388	—
4	2296	1324	3620	75	319	234	553	15	0.398	0.92	0.390	0.91
5	3534	2523	6057	65	714	384	1098	18	0.456	0.91	0.479	0.90
6	2480	1332	3812	65	439	317	756	20	0.386	0.90	0.383	0.87
7	2712	1530	4242	64	609	519	1128	27	0.399	0.90	0.355	0.92
8	2380	1618	3998	49	589	510	1099	27	0.447	0.91	0.431	0.89
9	2015	1588	3603	51	535	581	1116	31	0.467	0.94	0.428	0.95
10	2381	2003	4384	62	301	650	951 (1486)†	22 (34)†	0.501	0.91	0.447	0.88

* Calculated assuming H_m/H_c unchanged from initial value.

† Values in parentheses approximate the blood volume situation during the final hemodynamic observations (hour 8) and prior to transfusion (535 ml.)

TABLE 2. Estimates of Plasma Volume Replaced During Operation and Rates of Administration of Intravenous Fluid

Case	Plasma Volume				Intravenous Fluid (ml./kg./hr.)
	Calculated Loss (ml.)	Measured Change (ml.)	Difference		
			Ml.	Per cent	
1	281	145	136	48	3.7
2	463	202	261	56	2.5
3	502	253	249	50	2.6
4	360	319	41	11	—
5	437	714	−277	−63	1.7
6	506	439	67	13	1.8
7	858	609	249	29	3.0
8	652	589	63	10	2.1
9	716	535	181	25	2.0
10	985	301	512*	63*	4.0

* Corrected for plasma given with transfusion of blood.

A needle (19 gauge) was placed in the right radial artery percutaneously after induction of anesthesia for measurement of arterial pressure and for sampling.

Results

Initial values for blood volume (table 1) were within the range of normal.[11, 12] Initial values for H_m/H_c agreed both in average (0.91) and in range (0.89 to 0.94) with those observed in normal man.[10] Final values for blood volume indicated an 8 to 31 per cent reduction in blood volume. A reduction in H_c and H_m was observed in all cases except case 5, which suggests that some degree of plasma replacement had occurred in these nine patients. Final values for PV were less than initial values (table 1), which suggests that plasma replacement was not complete. The degree of plasma replacement was further examined in the following manner. PV lost was obtained by subtracting CV lost from BV lost (see Methods) and represents an estimate of the volume of plasma lost by hemorrhage. The measured change in PV (initial PV minus final PV) provided a value for the *actual* change in plasma volume. Accordingly, the volume of plasma replaced was obtained by difference (PV lost minus change in PV). The values obtained for each of these entities are listed in table 2 along with the associated rate of intravenous fluid administration. In case 10, the greatest degree of plasma replacement, both in volume (512 ml.) and relative to loss (63 per cent), was associated with the highest rate of fluid administration (4.0 ml. per kilogram per hour). In case 5, a degree of plasma volume reduction greater than could be accounted for by loss of whole blood was associated with the lowest rate of fluid administration (1.7 ml. per kilogram per hour). Final values for H_c and H_m in this patient were higher than initial values; this was not observed in any other patient. While these observations, at either end of the spectrum, suggest a correlation between rate of fluid administration and degree of plasma volume replacement, results in the eight other patients support but do not confirm a direct relationship.

Serial hemodynamic observations are presented individually (table 3) and as average change from initial observations (figs. 1 and 2). Initial values for cardiac output averaged 2.3 liters per minute per square meter (range, 1.8 to 3.1). Cardiac output and stroke index remained the same or increased as venous pressure decreased. While the average per cent change in venous pressure (fig. 1) appears to be progressive with time, the actual change (table 3) in pressure units was similar in short and long operations. Little change in heart rate was observed. Changes in systemic resistance were parallel to and directionally opposite to changes in cardiac output. Changes in arterial pressure were small and

variable. Collectively, other than a progressive reduction in central venous pressure, there was general hemodynamic stability. In case 8 between hours 6 and 7, with infusion of 600 ml. of 5 per cent glucose in 0.2 per cent NaCl in 5 minutes, cardiac output increased from 2.1 to 2.8 liters per minute per square meter, heart rate was unchanged, stroke index increased, and mean arterial and venous pressures increased from 90 and 8 to 110 and 9 mm. of mercury, respectively. These changes were not sustained and values at hour 7 were similar to those at hour 6. In case 10 after the last listed observation (hour 8), hemodynamics were observed 10 to 15 minutes after infusion of 535 ml. of blood in 10 minutes. Transfusion was associated with an increase in cardiac output to 2.9 liters per minute per square meter, no change in heart rate, increase in stroke index, and an increase in mean arterial and venous pressures to 110 and 6 mm. of mercury, respectively. In contrast to these observations, significant correlation did not exist, by inspection or by statistical analysis, between the degree of reduction of blood volume and the change in other variables in individual patients (table 4).

In individual patients, peripheral venous pressure (not tabulated) was 1 to 5 mm. of mercury higher than central venous pressure. This gradient was maintained throughout the period of observation and reductions of central venous pressure were associated with equivalent reductions in peripheral venous pressure. In all patients, peripheral and central venous pressures were lower in the awake, unanesthetized situation (range, 5 to 9 mm. of mercury) than after induction of anesthesia and institution of controlled ventilation (range, 7 to 15 mm. of mercury). A variable degree of respiratory alkalosis without significant alteration in the metabolic component was observed (not tabulated) in all patients (pH 7.40 to 7.60, arterial P_{CO_2} 17 to 29 mm. of mercury).

Discussion

The outstanding finding of this study was the general hemodynamic stability during operation in the presence of significant reductions in blood volume. Unreplaced blood loss, leading to reductions in blood volume of 10 to 30 per cent, was not associated with significant reductions in cardiac output or in arterial blood pressure even though anesthesia was of long duration and associated with an elevated mean airway pressure. These findings failed to confirm oft repeated generaliza-

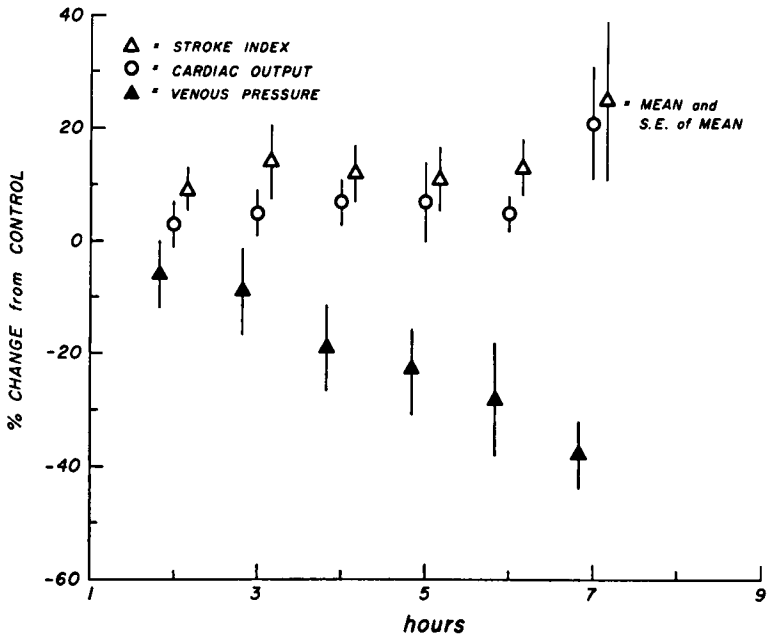

FIG. 1. Average changes, expressed as percentage change from initial values (hour 1), in stroke index (open triangle), cardiac output (open circle), and venous pressure (solid triangle) during ether anesthesia and unreplaced blood loss. Vertical lines indicate standard errors of the means.

TABLE 3. Serial Hemodynamics During Unreplaced Blood Loss in the Course of Operation Under Ether Anesthesia

Case	Hour	Cardiac Output (l./min./m.²)	Heart Rate (beats/min.)	Stroke Index (ml./m.²)	Mean Pressures (mm. Hg)	
					Arterial	Venous
1	1	2.8	80	35	95	7
	2	2.6	78	33	83	9
	3	2.7	72	37	86	8
	4	2.9	72	40	81	7
	5	2.6	63	41	87	7
2	1	3.1	87	36	90	12
	2	3.6	84	43	105	12
	3	3.7	78	47	99	11
	4	3.9	84	47	97	9
3	1	1.9	72	26	97	15
	2	2.3	63	36	97	13
	3	2.3	54	42	86	10
4	1	2.3	69	34	82	7
	2	2.5	65	39	84	6
	3	2.5	72	35	65	5
	4	2.6	60	43	85	3
5	1	2.1	69	31	117	13
	2	1.9	60	32	103	8
	3	2.1	66	31	101	7
	4	2.2	66	33	91	8
	5	2.0	66	30	81	7
	6	2.2	66	33	79	8
	7	3.0	66	45	92	6
	8	2.6	71	36	92	5
6	1	2.3	76	30	97	10
	2	2.3	66	35	92	11
	3	2.1	66	31	96	13
	4	2.5	66	38	93	12
	5	2.5	66	38	92	11
	6	2.4	66	37	86	11
	7	3.0	66	46	100	8
7	1	2.3	66	34	107	12
	2	2.2	72	31	113	10
	3	2.3	60	38	94	10
	4	2.2	72	30	106	9
	5	2.3	66	34	97	8
	6	2.6	60	42	89	8
8	1	1.8	62	30	121	13
	2	1.8	57	32	109	14
	3	1.9	54	35	102	14
	4	2.2	60	36	101	13
	5	2.5	69	37	99	9
	6	2.1	72	29	90	8
	7	2.2	68	32	94	7

TABLE 3.—(*Continued*)

Case	Hour	Cardiac Output (l./min./m.²)	Heart Rate (beats/min.)	Stroke Index (ml./m.²)	Mean Pressures (mm. Hg)	
					Arterial	Venous
9	1	2.3	72	32	99	7
	2	2.1	72	29	88	5
	3	2.1	72	29	91	6
	4	2.1	72	29	93	5
	5	—	72	—	101	5
	6	2.4	66	36	99	4
	7	—	66	—	91	5
	8	2.1	66	31	113	4
10	1	2.1	82	25	97	7
	2	2.4	84	28	94	7
	3	2.6	90	29	81	7
	4	2.3	90	26	90	6
	5	2.2	90	25	90	5
	6	2.0	—	—	—	—
	7	2.0	80	24	88	4
	8	2.0	95	21	85	3

tions such as "in the presence of a reduced blood volume (15 to 25 per cent), venous return to the heart is limited; filling of cardiac chambers is inadequate, resulting in a reduced cardiac output." [4]

Several mechanisms are believed to have been operative during the period of blood loss and to have served to promote hemodynamic stability. The maintenance or augmentation of stroke volume in the presence of reduced atrial pressure suggests increased ventricular distensibility or contractility or both. The latter has been observed [13] during ether anesthesia in man and is probably mediated by the reflex release of epinephrine and norepinephrine.[14] Failure of cardiac output to increase consistently during the period of study, in contrast to the results reported by Jones

TABLE 4. Correlation of Blood Volume Reduction With Other Observations

Case	Blood Volume Reduction		Changes (Final–Initial) in Other Observations				
	Ml.	Per cent	H_c	Cardiac Output (l./min./m².)	Heart Rate (beats/min.)	Mean Pressure (mm. Hg)	
						Arterial	Venous
1	344	8	−.019	−.2	−17	−8	0
2	595	12	−.028	+.8	−3	+7	−3
3	592	13	−.029	+.4	−18	−11	−5
4	553	15	−.008	+.3	−9	+3	−4
5	1098	18	+.023	+.5	+2	−25	−8
6	756	20	−.003	+.7	−10	+3	−2
7	1128	27	−.044	+.3	−6	−18	−4
8	1099	27	−.016	+.4	+6	−27	−6
9	1116	31	−.039	−.2	−6	+14	−3
10	1486*	34*	−.054	−.1	+13	−12	−4

* Corrected for transfusion of blood (535 ml.).

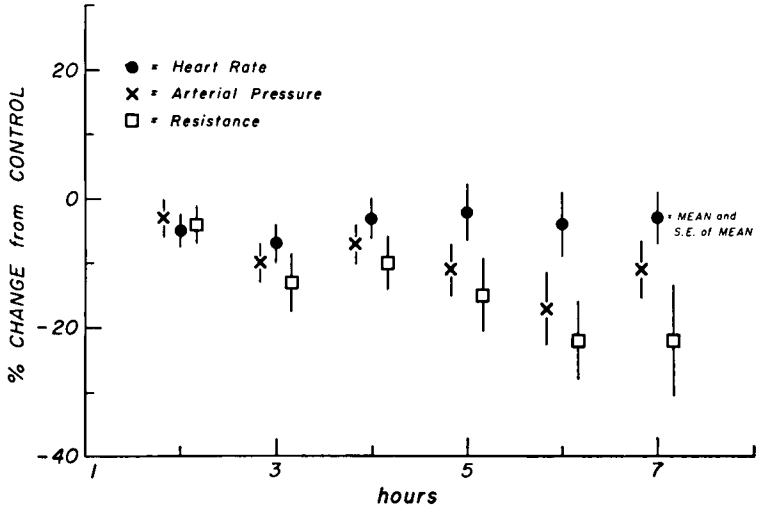

FIG. 2. Average changes, expressed as percentage change from initial values (hour 1), for heart rate (solid circle), arterial pressure (x), and resistance (open square) during ether anesthesia and unreplaced blood loss. Vertical lines indicate standard errors of the means.

and co-workers,[13] may be based on the blood loss and reduction in ventricular filling pressure that occurred in the present study.

The role of venomotor mechanisms in modifying the responses observed is less clear. It seems established that in intact man "distensibility and contractility of the veins contribute decisively towards the maintenance of an adequate central blood volume at a pressure sufficient to secure normal filling."[15] Furthermore, in the absence of active change in venomotor tone, the pressure-volume relationship of the venous system is 7 cm. of water (5.2 mm. of mercury) per liter of blood for a normal 70-kg. man.[15] Reduced distensibility of this system has been observed to occur in intact man in response to reduction in circulating blood volume,[16] overventilation with reduction in CO_2 levels,[17] and increased airway pressure.[18] In the present study, the reduction in venous pressure was about the same regardless of the reduction in blood volume over the range of 12 to 34 per cent of the initial blood volume. The reduction in venous pressure was generally less than that observed when similar volumes of blood are removed from man without active change in venomotor tone.[15] With transfusion, in one patient, venous pressure returned to the level observed prior to blood loss even though only one third of the loss was replaced. It is concluded from this indirect evidence that active changes in venomotor tone must have occurred. The data do not, however, allow conclusions as to the precise role of blood loss, reduced CO_2 levels, elevated airway pressure, duration of stimulus, or effect of anesthesia and other variables, including catecholamine levels, in determining the response.

Restoration of blood volume by hemodilution was less complete and more variable than expected.[2] Volume replacement by this mechanism was incomplete even for the plasma portion of the blood loss and appeared to be related closely to the rate of fluid administration. This may be a simple, transient dilution phenomenon rather than an active biologic process since there is no reason to believe that any of these patients were in negative water balance prior to or during the study and the hemodynamic response to acute increase in fluid therapy was not sustained in case 8. The overall hemodynamic pattern did not appear to be influenced significantly by rate of fluid administration. It is evident, however, that serial change in hematocrit of peripheral blood is an insensitive and unreliable index of quantity of blood lost and is subject to considerable influence by the rate of fluid administration.

The clinical implications of this study deserve comment. The respected position of ethyl ether as an anesthetic agent is documented by the remarkable hemodynamic stability observed in the presence of prolonged anesthesia and operation accompanied by sig-

nificant blood loss. The maintenance of cardiac output under these circumstances is considered to be evidence of the extent and appropriateness of compensatory mechanisms available to man during ether anesthesia and to account for the lack of correlation of degree of reduction in blood volume with change in cardiac output, heart rate, and arterial or venous pressure. Decisions about transfusion therapy in these patients were based primarily on *clinical* estimates of the adequacy of cardiac output and, in retrospect, seem to have been proper. Noteworthy features of the context of the present study include: light anesthesia with ether; slow, steady blood loss; superficial operative procedures; hyperventilation; the supine position; and removal of the superficial venous system of the operated extremity. The degree to which these observations and conclusions are appropriate to the conditions of abdominal or thoracic surgery involving the same or different anesthetic agents and techniques or to acute unreplaced blood loss is not evident at present.

Summary

Serial studies of hemodynamics and blood volumes have been carried out in 10 adults while they were undergoing extensive operations (3 to 9 hours) for varicose veins. Anesthetic management included: premedication with pentobarbital, meperidine, and atropine; induction with thiopental; maintenance with nitrous oxide and ethyl ether; and manual hyperventilation. Unreplaced blood loss occurred in all patients and total blood volume was reduced 8 to 31 per cent of the preoperative value. Hemoconcentration was observed in one patient who received intravenous fluids at the rate of 1.7 ml. per kilogram per hour. In the other patients with higher rates of administration of fluid, variable degrees of hemodilution were observed. The greatest degree of plasma volume replacement (63 per cent) was associated with the highest rate of fluid replacement (4.0 ml. per kilogram per hour). In all patients, the ratio of total body hematocrit to peripheral hematocrit observed preoperatively was little different from that at the end of operation.

During the period of unreplaced blood loss and reduction in blood volume, both peripheral and central venous pressures decreased. Cardiac output remained steady or increased slightly and heart rate was unchanged or decreased. No reductions in stroke index were observed. Total systemic vascular resistance varied inversely with changes in cardiac output and only small and variable changes in arterial pressure were seen. Both peripheral venomotor and central myocardial compensatory mechanisms are believed to be responsible for the degree of hemodynamic stability observed under these conditions of unreplaced blood loss.

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EXERCISE BY SMOKERS Exercise in smokers produced no changes in oxygen uptake or pulmonary function significantly different from exercise in non-smokers; however, there was a significant increase in the oxygen debt accumulation. Smokers showed a significantly greater increase in heart rate. Since these differences are apparently not related to ventilatory factors they may be due to circulatory or metabolic differences. (*Chevalier, R., and others: Circulatory and Ventilatory Effects of Exercise in Smokers and Non-Smokers, J. Appl. Physiol. 18: 357 (Mar.) 1963.*)

MESENTERIC ATHEROSCLEROSIS Postmortem examination of 88 unselected adults (43 men, 45 women) between the ages of 28 and 88 was carried out to determine the incidence of significant atherosclerosis in the mesenteric arterial tree (celiac, superior and inferior mesenteric arborizations) and to compare this with similar disease of the coronary arteries and abdominal aorta. In 68 cases (77 per cent) mesenteric atherosclerosis was found, with luminal stenosis in 49 instances. The vessels most frequently involved were the three main stems and the splenic artery. There was a positive correlation between severe mesenteric atherosclerosis and the incidence of myocardial infarction and there was a similar correlation with diabetes mellitus. There was not a good correlation between hypertension and the severity of mesenteric atherosclerosis. The presence of severe mesentric atherosclerosis was usually associated with the same changes in the abdominal aorta but the reverse was frequently not so. The finding of severe mesenteric atherosclerosis was associated with severe sclerosing coronary artery disease twice as frequently as the reverse. Also, there was fairly good correlation between coronary and abdominal aortic atherosclerosis. (*Reiner, L., Jimenez, F. A., and Rodriguez, F. L.: Atherosclerosis in the Mesenteric Circulation, Amer. Heart J. 66: 200 (Aug.) 1963.*)