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Research Article

PLASMA VOLUME AND "EXTRAVASCULAR THIOCYANATE SPACE" IN PNEUMOCOCCUS PNEUMONIA[1]

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Many published studies indicate by indirect measurement that fluid is retained during the course of pneumonia. In 1869, the weight and fluid balance of febrile patients, including a number suffering from pneumonia, were studied (1), and it was concluded that water was retained during the course of this disease. Similar conclusions were reached from studies of weight and serum protein concentration (2), weight alone (3 to 5), elasticity of tissue (6), and decrease in freezing point depression of serum (7). Some authors (8) studied the blood volume, by the method of Keith, Rowntree, and Geraghty (9), in 14 children suffering from "primary pneumonia" and calculated that the blood volume was increased as compared to normal standards for children of the same weight. In contrast, others (10) reported that the plasma volume as measured by the Congo red method was within normal limits in 65 patients with primary pneumonia. No control measurements were made in either study following recovery from the disease. In a review of the literature, no studies on extracellular fluid volume in pneumonia were found.

The present study was made on adult patients suffering from pneumococcus lobar pneumonia or bronchopneumonia. Plasma volume measurements were made on 52 patients of whom 46 recovered (Table I) and 6 died (Table VII). Measurements of the size of the "extravascular thiocyanate space" were made on 26 of the 46 recovered patients and on 5 of the fatal cases. All patients had definite symptoms and signs of pneumonia. The presence of pneumonia was confirmed by at least one x-ray photograph of the chest or by autopsy. The sputum and blood of every patient was examined bacteriologically. A type specific pneumococcus was isolated by the Neufeld method from the sputum in every case except one. The patients were treated with sulfapyridine, sulfathiazole, sulfadiazine, antiserum, or combinations of these. Patients suffering from heart disease and other chronic diseases were excluded from this study. Heart disease was diagnosed on the basis of an enlarged heart, a diastolic murmur, a history of angina pectoris, an abnormal electrocardiogram after recovery from pneumonia, or the presence of congestive heart failure. Since a study of the electrocardiographic changes occurring during the course of pneumococcus pneumonia was conducted at the same time on these same patients (11), at least one electrocardiogram was taken on every patient during pneumonia and following recovery in the non-fatal cases.

In all cases, the measurements during pneumonia were initiated within 2 hours of admission to the hospital and prior to the institution of any specific therapy. Following admission and during the experimental procedure, the patients were allowed to drink as much fluid (fat-free) as they desired. The patients were studied in a semi-recumbent position at an angle of about 30° from the horizontal. The recovered patients were restudied on the morning of the day that they were considered well enough to be allowed out of bed and the determinations were made prior to that event. The plasma volume in 20, and the "extravascular thiocyanate space" in 18 of the recovered patients were again determined following an interval of 1 week to 6 months. The measurements during recovery were made before breakfast, without restriction of fat-free fluid, with the patient in the same position (semi-recumbent). The patients who returned for a third measurement were studied under identical conditions.

[1] This study was aided by a grant from the John and Mary R. Markle Foundation.

METHODS

The plasma volume was determined by the T-1824 dye method (12), as modified for the Evelyn photoelectric microcolorimeter (13). The "total blood volume" was calculated from the plasma volume and the hematocrit. The latter value was the average of 4 hematocrit determinations, made on blood taken at the time of collection of the dye-free sample and at the time of the first, third, and sixth dyed samples. All hematocrits were determined on venous blood collected without stasis and centrifuged for at least 30 minutes at 3000 RPM.

In those patients in whom plasma volume and thiocyanate determinations were made, these measurements were performed simultaneously.[2] The thiocyanate method is modified from that of Crandall and Anderson (15) as follows:

The skin was infiltrated at the site of venipuncture with procaine (1 per cent) without epinephrine. A venipuncture was made and a control sample of blood was withdrawn without stasis by syringe through an 18 gauge needle. (All syringes, needles, and tubes were cleaned, dried, and sterilized by dry heat.) The syringe was disconnected, leaving the needle in place and the blood placed in a tube containing a small amount of mineral oil to prevent adherence of the clot to the walls of the tube. Through the same needle, 16 ml. of a 5 per cent sterile solution of sodium thiocyanate[3] were injected in 8 ml. amounts from each of 2 accurately calibrated syringes

[2] It has been demonstrated (14) that the simultaneous injection of sodium thiocyanate and T-1824 does not interfere with the subsequent determination of the concentration of either substance.

[3] We are indebted to the Division of Laboratories and Research of the New York State Department of Health for the preparation of a sterile 5 per cent solution of sodium thiocyanate.

TABLE I

Experimental data and pertinent clinical observations on 46 patients who recovered from pneumococcus lobar pneumonia

Case No.	Sex	Age	Day of disease on adm.	Pneu. type	Bact. (Pn. type)	Lobes	Surface area	Plasma volume			"Extravascular thiocyanate space"			Venous hematocrit			Red blood cell count			Hemoglobin		
								Adm.*	Rec.*	Post rec.	Adm.	Rec.*	Post rec.	Adm.	Rec.*	Post rec.	Adm.	Rec.*	Post rec.	Adm.	Rec.*	Post rec.
		years					*sq. m.*	*ml.*			*ml.*			*per cent*			*millions*			*grams*		
3	M	32	3	5	Neg.	LL	2.06	3520	3495					45.0	46.7		5.20	5.51		15.6	15.8	
4	M	31	5	5	Neg.	LL	1.77	3776	2798					42.9	49.0		4.70	5.00		12.3	14.0	
5	M	14	3	1	Neg.	RL	1.63	3635	2345	3710	12285	11625	13980	40.1	41.2	34.9	5.04	5.05	4.30	13.3	13.3	11.5
7	M	26	2	3&9	Neg.	LL	1.63	3193	2466					44.5	45.9		5.16	4.88		17.2	15.3	
8	M	26	5	10	Neg.	LL	1.98	3680	3560	3027	12180	12300		38.7	37.1	42.1	4.85	4.17	5.11	13.3	12.0	14.3
9	F	20	8	Unc.†	Neg.	LL	1.47	4260	3800		9840	8620		21.7	23.3		2.75	3.21		6.6	7.4	
10	M	42	6	3	Neg.	LL	1.68	2380	2710		12310	13410		42.9	44.0		4.22	4.56		14.5	15.0	
11	M	18	4	1	Neg.	RL	1.62	3205	2680	3024	11165	10587	10276	41.4	43.1	39.0	4.23	4.74	4.36	14.5	14.5	13.3
12	F	36	3	5	Neg.	LL		2480	2602					39.1	38.2		4.54	4.07		13.1	12.5	
16	F	31	3	8	Neg.	RL	1.57	2555	2158		8816	7792		40.9	43.1		4.52	4.82		13.5	15.0	
20	F	34	2	3	Neg.	RL LL	1.51	3980	3625	3978	10520	9675	8852	34.9	31.6	31.7	3.62	3.63	3.51	11.2	10.7	
21	M	21	3	1	Neg.	LL	1.63	2890	2213	2756	10970	9007	9784	41.2	45.5	45.8	4.86	4.96	5.56	13.9	15.2	15.6
26	F	56	5	7&21	Neg.	RU	1.71	3320	2960		12850	9970		35.2	36.1		3.66	3.74		11.3	11.8	
27	M	68	8.	7	Neg.	RU RM	1.86	2670	2235	2675	14830	13305	13600	39.2	42.3	41.1	4.25	4.74	4.46	13.1	14.0	13.9
29	M	42	2	3	Neg.	LL	1.50	2997	3335					42.9	37.5		4.58	3.96		13.4	11.6	
31	M	51	2	8	8	RL	1.68	2342	2215	3495	11688	10105	10475	44.9	42.4	40.4	4.63	4.53	4.61	14.4	13.3	12.9
32	M	49	4	1	Neg.	RL	1.70	3610	3908					38.0	34.4		3.74	3.80		12.0	11.3	11.3
36	M	39	2	1	1	LL	1.94	4275	3805	3693	15765	13345	13127	42.5	39.6	41.0	5.41	4.66	5.26	14.3	12.6	14.1
40	F	37	6	7	Neg.	RU	1.66	3225	2365	2400	10725	9865	10640	36.0	42.0	40.1	3.94	4.90	4.30	11.9	14.0	13.0
41	M	22	5	1	1	RL		2960	2975					41.7	40.7		4.80	4.58		13.3	11.5	
42	M	58	2	3	Neg.	RL LL	1.63	3890	3250	3130	12230	12280	13350	40.3	42.8	40.8	4.63	5.02	5.01	14.3	15.0	12.4
45	M	57	5	29	Neg.	RL	1.54	3550	2607		10670	9823		38.2	42.4		3.98	4.29		12.9	14.2	
46	M	62	2	3	Neg.	RL RU	1.75	3466	3421					46.4	43.4		4.95	4.70		13.3	12.6	
48	M	31	2	1	Neg.	Unk.	1.73	2872	3530					40.8	40.4		4.69	4.42		13.0	12.7	
57	M	53	3	12	Neg.	RL	1.47	3685	3565	3255	11325	10385	10955	36.2	36.6	37.9	4.18	4.07	4.37	12.4	12.1	12.4

* Immediately following recovery. † Unclassified.

TABLE I—*Continued*

Case No.	Sex	Age	Day of disease on adm.	Pneu. type	Bact. (Pn. type)	Lobes	Surface area	Plasma volume			"Extravascular thiocyanate space"			Venous hematocrit			Red blood cell count			Hemoglobin		
								Adm.	Rec.*	Pos rec.	Adm.	Rec.*	Post rec.	Adm.	Rec.*	Post rec.	Adm.	Rec.*	Post rec.	Adm.	Rec.*	Post rec.
		years					*sq. m.*	*ml.*			*ml.*			*per cent*			*millions*			*grams*		
58	M	38	1	8	Neg.	RL		3590	2931					42.8	44.6		4.80	4.70		12.7	14.9	
59	M	26	2	1	Neg.	RL	1.63	2750	3258					42.1	43.8		4.70	4.45		13.6	14.0	
60	M	44	2	1&7	Neg.	RM RL	1.61	2380	1780		13447	12795		41.3	41.4		4.06	4.21		14.0	14.8	
61	M	46	6	1	Neg.	LL	1.73	3470	3658	2692	14030	12262	13888	37.2	32.4	35.8	4.48	3.62	4.36	13.6	10.3	11.7
65	M	39	3	1	Neg.	RU	1.74	3013	2402					42.7	45.6		4.18	4.50		13.6	14.0	
68	M	58	3	1	1	RL	1.70	3524	3142					36.5	39.8		3.93	4.26		11.2	11.4	
69	F	32	4	18	Neg.	LL	1.94	2900	2985	3150	13020	12035	12770	38.6	38.5	40.8	4.44	4.28	4.93	13.3	12.8	14.0
70	M	34	1	7	Neg.	RL		3208	3020					43.5	42.6		5.03	4.90		12.3	13.3	
73	M	15	2	1	Neg.	LL	2.15	4180	3600					37.4	42.6		4.00	4.88		10.9	13.7	
76	M	28	1	8	Neg.	LL	1.58	2653	2207	2575	13837	12293	12995	45.0	47.1	44.9	5.57	5.61	5.21	15.2	15.4	14.5
77	M	57	5	1	Neg.	RL	1.73	3820	3130	3593	15470	13040	16430	40.4	38.6	38.9	4.23	4.15	3.98	13.2	12.9	12.2
78	M	49	7	7	Neg.	RU RM	1.61	2440	2595	2320	14180	13535	12640	36.0	36.0	41.3	3.54	3.59	4.17	12.2	11.8	14.1
81	M	36	6	1	Neg.	RU	2.22	6046	4270	4820	27594	15750	15080	41.2	36.8	40.8	4.59	4.01	4.59	14.0	11.9	13.7
82	M	57	2	3	Neg.	LU LL	1.64	4475	3025	3790	14650	16975	13710	38.2	31.2	40.5	4.11	3.13	4.61	12.1	9.3	13.4
83	M	48	3	7	Neg.	RM RL	1.69	3326	2618					35.6	35.1		3.55	3.70		10.9	10.4	
85	M	50	3	14	Neg.	RM RL	1.63	2745	2550		10655	9990		45.6	44.2		4.69	4.52		15.0	14.1	
86	F	48	2	11	Neg.	LL		3180	2263					36.5	37.3		4.00	4.04		11.9	11.2	
87	M	15	3	1	1	RL	1.47	2970	2320					40.5	43.3		4.20	4.45		12.9	12.9	
90	M	48	6	7	Neg.	RU RM	1.55	1992	1847	1950				41.4	42.4	39.7	4.34	4.77	4.50	14.6	15.0	15.0
92	F	15	5	11	Neg.	RL	1.66	3575	2879					32.3	37.1							
94	F	39	3	8	8	RU	1.56	2320	2080	2718	10230	7390	8812	35.0	38.2	36.0	3.85	4.28	4.29	10.9	11.7	11.3

* Immediately following recovery.

(10 ml. capacity). Following injection and before disconnecting the syringe from the needle, each syringe was washed twice by drawing back the plunger, filling the syringe with blood, and reinjecting the contents of the syringe. Through the same needle, 10 ml. of a 0.1 per cent solution of T-1824 were injected from a third calibrated syringe (10 ml. capacity) and the syringe washed as indicated above.

After an interval of 20 minutes, a venipuncture with an 18 gauge needle was performed in the opposite arm, following procaine infiltration of the site. Dyed specimens were collected without stasis at 3-minute intervals until a total of 6 were obtained and placed in tubes containing mineral oil to prevent adherence of the clot. An additional specimen for thiocyanate determination was taken 1 hour later in the first 10 patients but since the thiocyanate concentration of the serum was not significantly different at this time, this practice was discontinued. Ten ml. of sterile physiological saline solution were slowly injected during each of the intervals between the collection of samples to keep the needle patent. The blood was allowed to clot by standing at least 45 minutes before centrifuging at 2500 RPM for one-half hour. The serum was pipetted off, placed in clean tubes without oil, and recentrifuged for an additional half-hour at 2500 RPM. The serum was again pipetted off and the concentration of T-1824 in the serum, now free from red blood cells and oil, was determined (13).

Following the determinations of the plasma concentration of T-1824, 1 ml. of 20 per cent trichloroacetic acid was added to 1 ml. of each of the 7 serum samples. The contents of the tubes were thoroughly mixed by inversion and were centrifuged at 2500 RPM for one-half hour or until a clear supernatant fluid was obtained. From each of the supernatant fluids, 1 ml. was transferred to a separate Evelyn macrocolorimeter tube and 8 ml. of distilled water were added to each. The center setting on the colorimeter was obtained (filter No. 490) by adding 1 ml. of a 5 per cent solution of ferric nitrate [4] to the control sample, mixing thoroughly, and reading immediately. The test specimens were treated in similar fashion. (Immediate readings were made since the color fades rapidly in the presence of light.) The concentration of sodium thiocyanate in mgm. per 100 ml. of serum was

[4] Prepared by the method of Crandall and Anderson (15).

readily calculated from a conversion graph prepared by the determination (by the same method) of known concentrations of sodium thiocyanate in serum. The total available fluid was calculated by the extrapolation method (16).

Duplicate red blood cell counts and hemoglobin determinations were made from venous blood collected at the time of the first venipuncture and placed in tubes containing a mixture of dry potassium and ammonium oxalate which causes no change in cell volume (17, 18) (ammonium oxalate—6 mgm., and potassium oxalate—4 mgm. per 5 ml. of blood). Certified pipettes and counting chambers were used for the red blood cell counts. The hemoglobin was determined in the Evelyn macrocolorimeter by the alkaline hematin method (19).

DEFINITION OF "EXTRAVASCULAR THIOCYANATE SPACE"

"Extravascular thiocyanate space" for the purposes of this paper is expressed in ml. of fluid and is defined as that value obtained when the plasma volume, as determined by the method of Gibson and Evans (12) (modified by Gibson and Evelyn (13)), is subtracted from the "total available fluid" volume determined by the sodium thiocyanate method described in this paper. This value is introduced for convenience in order to indicate fluctuations in body fluid, independent of variations in plasma volume. This term is not entirely satisfactory since it disregards the small percentage of sodium thiocyanate which is taken up by the red blood cells within the cardiovascular system. In this connection, it is of interest that there were no significant changes in the red blood cell count, the hematocrit, or the hemoglobin content in the blood of these same patients during pneumonia in comparison to similar measurements performed immediately following recovery (Table II). The mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration are, therefore, unchanged during the disease. However, as will be indicated later, the "total red cell volume," as calculated from the plasma volume and venous hematocrit, was increased during pneumonia. Direct determinations of total red blood cell volume were not performed in this study.

TABLE II

Mean venous hematocrit, red blood count, and hemoglobin of 45 pneumonia patients at the time of admission to the hospital and immediately following recovery from pneumnia*

Measurement	Mean of 45 cases		Difference in means on admission and recovery	Difference divided by standard error
	During pneumonia†	Immediately following recovery		
Venous hematocrit (*per cent*)	39.8	40.2	−0.4	0.9
Red blood count (*millions*)	4.39	4.40	−0.01	0.2
Hemoglobin (*grams*)	13.04	12.96	+0.08	0.1

* These data are not available for one of the 46 patients included in the study (Case No. 92).

† At time of admission to the hospital.

PLASMA AND "TOTAL BLOOD VOLUME" IN RECOVERED CASES

The mean plasma volume was increased by 387 ml. to 3282 ml. during pneumonia over the recovery value of 2895 ml., an increase of 13.4 per cent (Table III). Since the mean hematocrit was not significantly changed (Table II), the "total blood volume" was 5538 ml., 13.8 per cent greater during pneumonia than the recovery value of 4868 ml.

It is appreciated that theoretically (20) the conversion of plasma volume to "total blood volume" by the use of the venous hematocrit introduces errors due to the changing proportions of cells and plasma in blood vessels of various sizes. This error would tend to vary with redistribution of blood between blood vessels of various sizes during pneumonia. Moreover, a personal communication (21) indicates that "during the normal resting state there is probably a linear relationship between changes in the venous hematocrit and red blood cell volume as determined by radioactive iron. There is also in the resting state a fairly constant relationship between red blood cell volume determined by radioactive iron and red blood cell volume as determined by the dyed plasma hematocrit technique. This relationship, however, may become seriously altered in disease states and in peripheral vascular collapse so that the red blood cell volume determined by the dyed plasma hematocrit technique would not reflect real changes." The "total blood volume" measurements have been calculated and are reported but they are regarded with suspicion and future data on this point will be necessary before the data on the "total blood volume" can be interpreted.

TABLE III

Mean volume of plasma, "total blood," total available fluid, and "extravascular thiocyanate space" of pneumonia patients on admission to the hospital and immediately following recovery

Measurement (volume)	Number of cases	Mean volume		Mean increase in volume during pneumonia*	Increase during pneumonia	Difference divided by standard errror
		During pneumonia*	Immediately following recovery			
		ml.	*ml.*	*ml.*	*per cent*	
Plasma	46	3,282	2,895	+ 387	+13.4	5.3
"Total blood"	46	5,538	4,868	+ 670	+13.8	5.8
Total available fluid	26	16,234	14,322	+1,912	+13.4	3.8
"Extravascular thiocyanate space"	26	12,895	11,468	+1,427	+12.4	3.1

* At time of admission to the hospital.

In those patients in whom a third determination was performed, at an interval of 1 week to 6 months following the second determination, the plasma volume and "total blood volume" values were intermediate between those obtained during pneumonia and immediately following recovery from the disease. Thus, in the 20 patients in whom a third determination was performed, the mean plasma volume during pneumonia was 3380 ml., which decreased to 2883 ml. immediately following recovery, and returned to 3138 ml. in the post-recovery period (Table IV). A similar change occurred in the "total blood volume" when calculated from the plasma volume and the venous hematocrit. The mean "total blood volume" during pneumonia was 5683 ml., which decreased to 4787 ml. immediately following recovery and increased to 5253 ml. in the post-recovery period.

TOTAL AVAILABLE FLUID VOLUME AND "EXTRAVASCULAR THIOCYANATE SPACE" IN RECOVERED CASES

The mean total available fluid volume was 16,234 ml. during pneumonia, an increase of 1912 ml. (or 13.4 per cent) over the recovery level of 14,322 ml. (Table III). When the mean plasma volume of these 26 cases was subtracted from the mean total available fluid volume, similar changes were noted in the "extravascular thiocyanate space." This measurement was 12,895 ml. during pneumonia, an increase of 1427 ml. (or 12.4 per cent) over the recovery value of 11,468 ml. (Table III).

TABLE IV

Mean volume of plasma, "total blood," total available fluid, and "extravascular thiocyanate space" of pneumonia patients at the time of admission to the hospital, at the time of recovery, and following recovery from pneumonia

	Plasma	"Total blood"	Total available fluid	"Extravascular thiocyanate space"
No. cases	20	20	18	18
Mean volume (*ml.*)				
On admission*	3,380	5,683	17,024	13,584
Immed. following recovery	2,883	4,787	14,753	11,859
Post recovery	3,138	5,253	15,508	12,298
Difference in mean volume (*ml.*)				
Bet. adm.* and recovery	497	896	2,271	1,725
Bet. adm.* and post recovery	242	430	1,516	1,286
Bet. recov. and post recovery	255	466	755	439
Difference/standard error				
Adm.* and recovery	4.3	4.3	3.3	2.7
Adm.* and post recovery	2.1	2.2	2.0	1.9
Recov. and post recovery	2.1	2.5	2.1	1.3

* During pneumonia.

When a third determination of the total available fluid volume and "extravascular thiocyanate space" was performed in the post-recovery period, at the same time that the plasma volume and total blood volume measurements were made, the following changes were noted. Among the 18 cases on whom such measurements were performed, the mean total available fluid volume on admission was 17,024 ml., which decreased to 14,753 ml. immediately following recovery, and increased in the post-recovery period to 15,508 ml. Similarly in the same 18 patients, the mean "extravascular thiocyanate space" during pneumonia contained 13,584 ml. which decreased to 11,859 ml. immediately following recovery and increased to 12,298 ml. in the post-recovery period (Table IV).

It is of interest that the relative change in the volume of fluid within the cardiovascular system is similar to that occurring outside of that system in the "extravascular thiocyanate space" (Table III).

It is evident from the analysis of the data on patients upon whom 3 determinations were performed that the decrease in volume occurring immediately following recovery from pneumonia is greater than that necessary to return the patient's body fluid to normal levels.

TABLE V

*Number of cases and direction of change in volume of plasma, "total blood," total available fluid, and "extravascular thiocyanate space" of pneumonia patients from "immediately following recovery" to "during pneumonia"**

Measurement (volume)	Number of cases			
	Larger during pneumonia* than at time of recovery	Less during pneumonia* than at time of recovery	No change	Total
Plasma	36	10	0	46
"Total blood"	38	8	0	46
Total available fluid	23	2	1	26
"Extravascular thiocyanate space"	22	4	0	26

* At the time of admission to the hospital.

Table V indicates that the change in the various measurements in most of the patients was in the same direction as the change in the mean measurements. Those changes of plasma volume which were in the opposite direction were relatively small. The distribution of the changes in plasma volume is shown in Figure 1

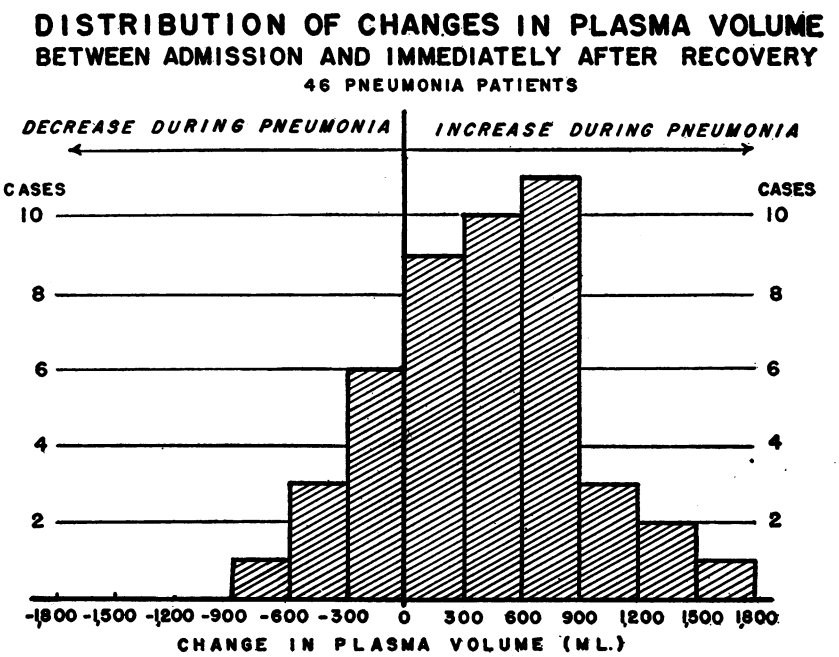

FIG. 1

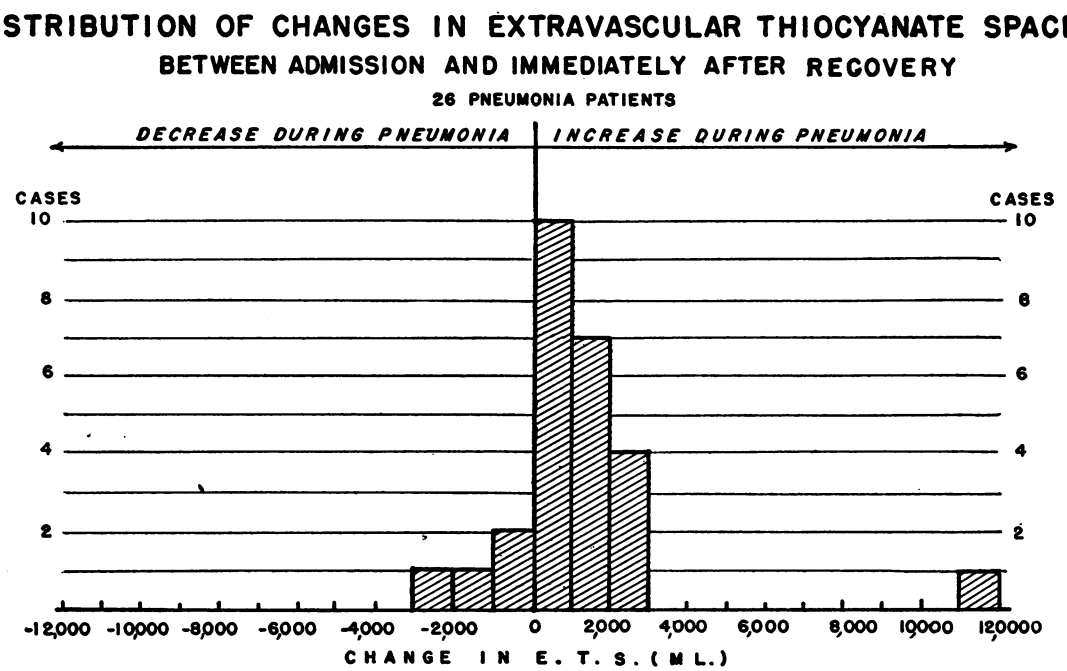

FIG. 2

and that of "extravascular thiocyanate space" in Figure 2.

The high order of statistical significance of these observations is confirmed by the ratios of the difference to the standard error indicated in the last column of Table III.

In most of the non-fatal patients studied, the measurements of height and weight on recovery are available. By means of the nomogram of Boothby and Sandiford (22), the surface areas of the patients were calculated (Table I). From this calculation, the mean changes in plasma volume, "total blood volume," total available fluid volume, and "extravascular thiocyanate space" per square meter of body surface area are similar (Table VI) to the mean of the observed measurements (Table III).

FATAL CASES

In the 6 patients who died from pneumonia, the mean plasma volume of 2547 ml., at the time of admission to the hospital, was strikingly different from the mean plasma volume, during pneumonia, of 3282 ml. in the 46 patients who recovered (Table VII). This difference is statistically significant. The changes in the "total blood volume" of these 6 patients showed a similar trend (Table VII) although the results

TABLE VI

Mean volume of plasma, "total blood," total available fluid, and "extravascular thiocyanate space" per square meter of body surface "during pneumonia" and "immediately following recovery"*

Measurements per square meter of body surface (volume)	No. cases	Mean volume		Mean increase in volume during pneumonia*	Change	Difference divided by standard error
		During pneumonia*	Immediately following recovery			
		ml.	*ml.*	*ml.*	*per cent*	
Plasma	41	1,942	1,719	+223	+13.0	5.0
"Total blood"	41	3,277	2,879	+398	+13.8	5.7
Total available fluid	26	9,568	8,493	+1075	+12.7	4.5
"Extravascular thiocyanate space"	26	7,585	6,796	+789	+11.6	3.6

* At the time of admission to the hospital.

TABLE VII

Volume of plasma, "total blood," total available fluid, and "extravascular thiocyanate space" of fatal cases of pneumonia at the time of admission to the hospital

Case number	Volume			
	Plasma	"Total blood"	Total available fluid	"Extravascular thiocyanate space"
	ml.	*ml.*	*ml.*	*ml.*
102	2,300	4,060	15,540	13,240
105	2,584	4,575	14,480	11,896
107	2,170	3,780		
110	3,342	5,885	14,700	11,358
112	2,828	5,600	16,600	13,772
114	2,060	3,995	13,330	11,270
Mean	2,547*	4,649*	14,930†	12,307†
Mean during pneumonia for recovered cases	3,282‡	5,538‡	16,234§	12,895§
Difference	−735	−889	−1,304	−588
Difference divided by standard error	3.5	2.4	1.4	0.8

* Mean of 6 cases. ‡ Mean of 46 cases.
† Mean of 5 cases. § Mean of 26 cases.

are not so significant. Determinations of total available fluid and "extravascular thiocyanate space" were performed in 5 of the 6 fatal patients. The results show a similar trend but are not statistically significant. In each of the 6 fatal cases in this study, the pneumonia involved more than one lobe.

Although the plasma volumes of the fatal cases in this study are similar to those of the 6 cases of pneumonia (in circulatory collapse) reported by others (23), their conclusions are not supported by this study. In that study, the plasma volume in 6 patients was considered normal in comparison with normal standards of patients of the same height, while in this study the comparison is made with the increased plasma volume due to pneumonia in recovered patients of similar size. Since most of the patients who died had clinical evidence of peripheral vascular collapse at the time of admission to the hospital, it is believed that the plasma volume in the fatal cases represents the effect of peripheral vascular collapse superimposed on the changes due to the pneumonia *per se*.

VALIDITY OF EXPERIMENTAL PROCEDURES

In order to determine whether the changes reported represent true changes in the volume of body fluid, or whether they are due to a loss of the testing substances in the exudate of the pneumonic lung, the following calculations and procedures were performed: The changes occurring in plasma volume and "extravascular thiocyanate space" in patients with multilobar involvement were compared with the changes in those with unilobar involvement. Ten patients with multilobar involvement during pneumonia showed a mean increase of plasma volume per square meter of body surface area of 268 ml., while 30 patients with unilobar involvement showed a mean change of 228 ml. Seven patients with multilobar involvement showed a mean change of 163 ml. in "extravascular thiocyanate space" per square meter of body surface area, while the change in 19 patients with unilobar involvement was 1020 ml. It is of interest that all the fatal cases had multilobar involvement and the plasma volumes of those patients were among the lowest recorded in this study. If the changes observed were due to loss of the testing substances in the exudate of the pneumonic lung, one would expect greater increases in these measurements in patients who had multilobar involvement. Additional evidence was obtained by the intravenous injection of 90 ml. of 0.1 per cent solution of T-1824 (9 times the amount used for plasma volume determination), a few hours prior to death in 3 patients who died of pneumonia. When the lungs were examined post mortem, no dye was visible in the gross specimens of either the pneumonic or uninvolved lungs. Similarly, 32 ml. of sodium thiocyanate (twice the amount used for total available fluid determination) were injected intravenously in 3 other pneumonia patients before death. Equal volumes (by displacement of water) of normal and pneumonic lung tissue contained similar amounts of sodium thiocyanate per unit volume of tissue. Finally, in each case when the concentration of the testing substance was plotted against time, a linear relationship existed and the slope of the "disappearance curve" was similar to those obtained in normal individuals by these methods. The evidence indicates that

the changes recorded in this study were not due to a loss of the testing substances in the exudate of the pneumonic lung.

FACTORS AFFECTING PROGNOSIS IN PNEUMONIA

From the data in Table I, calculations were made to determine whether the various factors which affect prognosis in pneumococcus lobar pneumonia were associated with the changes in plasma volume and "extravascular thiocyanate space." In order to rule out variations in the size of the patients, these analyses were made on calculations based on the values per square meter of body surface area. The mean increases occurring during pneumonia in plasma volume and "extravascular thiocyanate space" per square meter of surface area, over the levels determined immediately following recovery, were not influenced by sex, age (under 40 years *vs.* 40 years and over), pneumococcus type (types 1, 3, 5, 7 and 8 *vs.* other types), or duration of disease on admission to the hospital (1 to 3 days *vs.* 4 to 8 days). As noted in the previous paragraph, the change in plasma volume was not influenced by the number of lobes involved (unilobar *vs.* multilobar involvement) while the change in "extravascular thiocyanate space" was greater in the unilobar cases. There were only 5 patients with bacteremia in the study and that number was too small to determine the significance of the relationship of bacteremia to the changes noted.

CLINICAL IMPLICATIONS

This study indicates that pneumonia patients have more fluid than "normal" both within the cardiovascular system and in the extracellular spaces of the body. Many reports in the literature indicate that this increase in fluid is accompanied by a decrease in the concentration of solutes in the blood of pneumonia patients. Thus, the concentrations of chloride (7, 24 to 28), calcium (24, 29), phosphorus (30), magnesium (24), total base (7), amino acids (31), and cholesterol (32) have been reported as diminished during pneumonia. This decrease in solutes, accompanied by an increase in fluid, points to a disturbed osmotic equilibrium in pneumococcus pneumonia. Moreover, the increase of plasma volume in pneumonia indicates that the total amount of circulating solutes is changed relatively less than is indicated by the concentration of such solutes in the blood of pneumonia patients (or may be unchanged).

The increase of plasma volume during pneumonia probably plays a significant rôle in, and provides an additional explanation (in addition to anoxic anoxia and increase in metabolism) for, the precipitation of congestive cardiac failure in cardiac patients suffering from pneumonia. It suggests that caution should be exercised in the administration of fluids to cardiac patients suffering from pneumonia, even if the patient has had no previous attack of congestive cardiac failure.

The decrease in plasma volume and "extravascular thiocyanate space" immediately following recovery may prove of interest in a consideration of the circulatory readjustments occurring in convalescence.

SUMMARY AND CONCLUSIONS

1. Observations on the plasma volume, "extravascular thiocyanate space," and correlated measurements of the peripheral blood in 52 cases of pneumococcus pneumonia are presented.

2. The mean plasma volume and the mean "extravascular thiocyanate space" are significantly increased during pneumonia, and decrease to levels below normal immediately following recovery.

3. The mean plasma volume in fatal cases of pneumonia is significantly lower than similar measurements made on non-fatal pneumonia patients. This finding correlates with the clinical observation that these cases were suffering from peripheral circulatory failure.

4. The venous hematocrit, red blood cell count, hemoglobin level, and the determinations based on them (mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration) are unchanged during pneumonia.

5. The increase in plasma volume indicates that the total circulating solutes are diminished less than would appear from the measurements of the concentration of such solutes.

6. Increase in plasma volume during the acute phase of pneumonia offers a possible explanation for the precipitation of congestive heart failure

in cardiac patients suffering from pneumonia. The therapeutic implications of these observations are emphasized.

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