BLOOD VOLUME IN FEVER

By HERBERT C. SOULE, THOMAS E. BUCKMAN and DAN C. DARROW

(From the Pediatric Service of the Boston City Hospital and Washington University and St. Louis Children's Hospital)

(Received for publication October 4, 1927)

It has long been recognized that there are disturbances in water metabolism during fever, and increasing the water intake is now the most universally applied therapeutic measure used in controlling fever. The present study was undertaken to determine whether during fever there are fluctuations in blood volume that might be considered as reflections of the disturbed water metabolism.

In general, there is retention of water by the body as a whole during fever and release of this water again after defervescence. In 1869, the work of Leyden (1) demonstrated this as well as the increased heat production during fever. These facts have been rediscovered a number of times and gradually knowledge has emerged as to where the water retained during fever is stored. Water retention during primary pneumonia in children was demonstrated by weight charts (Lussky and Friedstein (2)). By means of an elastimeter water retention in the skin of ten cases of pneumonia in children was shown by Maver and Schwartz (3). Babies with fever excrete water given by mouth more slowly than normal babies (Hirsch (4)) and this seems to be due to actual water retention. Studies of scarlet fever show that the weight remains constant or that there is a slight gain in weight during the period of fever and this is accompanied by a positive chloride balance and dilution of the blood as measured by the serum protein concentration (Oppenheimer and Reiss (5)). During fever a gain in weight is accompanied by a lowering of the concentration of the serum protein but during convalescence there may be a gain in weight with a constant serum protein concentration. The authors interpreted the results to mean retention of water and salt during fever accompanied by a moderate blood dilution. Similar results were found in pneumonia (Sandelowsky (6)) except that in some of the

more severe cases, the author felt that part of the decrease in serum protein concentration was due to consumption of the proteins. Peabody (7) demonstrated a retention of chlorides, sodium and calcium and an increased excretion of phosphorus and magnesium during pneumonia. By analyses of the tissues, he came to the conclusion that the chloride retention could not be accounted for either by the pneumonic exudate or storage in increased concentration elsewhere and therefore was lead to assume a generalized storage of water throughout the body. Thus previous studies of water metabolism seem to favor the view that during fever water and salts are retained diffusely throughout the body.

It is not known why water should be held in the body during fever. The retention of water and of salts are probably ultimately parts of the same process. Nitrogen split products may play a part in the holding of water. Cook (8) showed a rather sudden release of nitrogen products in the urine after the crisis in lobar pneumonia. This was shown not to originate from the exudate alone for it was more than could be accounted for in that manner. Whipple and Cooke (9) found a large increase in the urinary nitrogen output in dogs in which they had induced fever by sterile abscesses or by proteose intoxication. The increased nitrogen output comes with defervescence. Little is known of what part nitrogen split products play in the retention of water during fever, but they do not seem to play an important rôle since changes in the distribution of water between the tissues and blood may be brought about by conditions which do not lead to cell destruction.

Barbour (10) and his co-workers have studied the effects of warm and cold environments on the water content of the blood, serum and tissues of dogs. Exposure to cold resulted in a concentration of the blood and serum and an increase in the water content of the subcutaneous tissues and muscles. Warm environments, except those that are so warm as not to permit the body to maintain its normal temperature, dilute the blood and serum with water and salts. As this effect could be brought about by warming or cooling the brain alone, the workers felt that the changes were under the control of the central nervous system. Bancroft (11) and his co-workers found that warm environments lead to an increase in the blood volume of about 20 per

cent. Thus the body seems to be able to shift water into or out of the blood stream by mechanisms involving no tissue injury.

In the present paper the effect of fever on the blood volume was the chief subject of investigation. In addition to the cases of typhoid fever, pyelitis, etc., a number of cases of primary pneumonia in children are used as examples of the effect of fever. This raises the question of the effect of pulmonary insufficiency on blood volume and blood concentration. True uncompensated deficiency of pulmonic function is rare. An ideal example would be a state in which the circulation through the lungs was normal but oxygen was not readily absorbed and carbon dioxide not readily excreted. Certain types of pulmonary edema approximate this condition. The war gases produce an intense edema of the lungs, and accompanying this there is marked concentration of the hemoglobin (Underhill (12)). A similar concentration of the hemoglobin was found by Underhill and Ringer (13) in post-influenzal bronchopneumonia. Excepting states of dehydration and shock, the concentration of the hemoglobin found by Underhill and Ringer is greater than is met in any other pathological state. In ordinary lobar pneumonia, blood concentration does not occur and the changes seen need not be interpreted as caused by pulmonic deficiency. The characteristic finding in pneumonia is that the venous and arterial blood have oxygen and carbon dioxide contents which differ from each other less than under normal conditions. It is obvious that if the circulation is very rapid the arterial blood will not have time to lose its oxygen; the tissues will have no need to absorb all the oxygen offered by the rapidly circulating blood, and the blood may not have time to become saturated with oxygen in the lungs. If there were difficulty in aerating the blood or in excreting carbon dioxide, one would find both an increased venous and arterial oxygen-unsaturation, and the carbon dioxide would accumulate in the blood. For the above reasons, rapid circulation seems to be the best explanation for the chief changes in the blood in pneumonia. If this reasoning is correct, other fevers may produce similar changes and it seems justifiable to use primary pneumonia as an example of fever.

The methods used in this investigation are the same as those used in the previous one (15). Blood volumes and chlorides were determined on twenty cases of primary pneumonia in children, seven cases

TABLE 1

Case	Date	Age	Sex	Weight	Diagnosis	Fever	Cell volume	Blood volume—total			Blood volume per kilogram			Chlorides per 100 ml.			Serum protein		
								Blood	Plasma	Cells	Blood	Plasma	Cells	Blood	Plasma	Cells	Per cent	Grams	Grams per kilogram
		yrs.		*kg.*			*per cent*	*ml.*	*ml.*	*ml.*	*ml.*	*ml.*	*ml.*	*mg.*	*mg.*	*mg.*			
1	May 29, 1923	12	F.	24.0	Typhoid	+	34.1	2,256	1,488	768	94.0	62.0	32.0						
1	May 30, 1923	12	F.	24.5	Typhoid	+	33.0	2,130	1,427	703	186.6	57.8	28.7	499	576	342			
2	May 29, 1923	8	M.	15.5	Typhoid	+	33.0	1,375	922	454	88.8	59.5	29.2	308	449	240			
2	June 15, 1923	8	M.	16.2	Convalescent	0	36.3	1,027	654	373	63.4	40.4	23.0	466	516	377			
3	September 22, 1923	11	M.	32.0	Typhoid	+	22.4	2,240	1,740	500	70.0	54.4	15.6	482	540	282			
4	June 18, 1923	5	F.	16.3	Pyelitis	+	36.2	1,410	900	510	86.5	55.0	31.3	500	574	369			
5	June 28, 1923	6	F.	20.0	Pyelitis	+	32.8	1,725	1,160	565	86.2	58.0	28.2	474	532	353			
6	July 27, 1923	7	F.	17.0	Pyelitis	+	29.0	1,520	1,080	440	89.4	63.5	25.9	496	532	407			
7	September 14, 1923	8	M.	23.4	Pyelitis	+	30.1	1,952	1,315	587	83.5	58.3	25.1	523	580	389			
8	July 19, 1923	9	F.	21.5	Pyelitis	+	37.0	1,562	984	578	72.6	45.7	26.8	448	529	310			
9	January 1, 1923	10	F.	28.4	Pyelitis	+	36.0	1,575	1,008	567	55.6	35.5	28.7	498	610	272			
10	July 4, 1923	10	F.	29.0	Pyelitis	0	38.0	2,340	1,450	890	80.7	50.0	30.7	485	557	368			
11	May 16, 1923	10	M.	27.3	Thoracic empyema	+	33.0	1,888	1,265	623	69.2	46.4	22.8	490	591	285			
12	May 23, 1923	12	F.	34.5	"Influenza"	+	39.0	2,546	1,553	993	73.8	45.0	28.7	464	542	343			
13	May 26, 1923	4	M.	14.0	Tuberculosis meningitis	+	49.0	1,498	764	734	107.0	54.5	52.4						
14	June 15, 1923	8	M.	19.5	Encephalitis	+	35.0	1,635	1,062	572	83.8	54.5	29.3	506	574	380			
15	June 20, 1923	1	M.	13.1	Pneumonia	+	31.2	1,160	800	360	88.6	61.0	27.7	491	552	356			
16	December 12, 1922	1.5	F.	12.2	Pneumonia	+	31.0	905	625	281	74.0	51.0	23.0						

17	June	6, 1923	4	M.	20.9	Pneumonia	+	35.0	1,870	1,215	655	89.4	58.1	31.3	523	598	386			
18	June	25, 1923	4	M.	15.6	Pneumonia	+	36,0	1,275	816	459	81.7	52.3	29.4	450	524	319			
19	June	5, 1923	6	M.	25.0	Pneumonia	+	57.1	3,160	1,355	1,805	126.0	54.2	72.5	448	494	414			
20	June	1, 1923	7	M.	18.2	Pneumonia	+	30.3	1,542	1,077	464	84.7	59.2	25.4	427	487	287			
21	July	3, 1923	7	M.	16.4	Pneumonia	+	32.0	1,225	833	392	74.6	50.7	23.9	435	494	312			
22	July	7, 1923	7	M.	19.0	Pneumonia	+	35.0	1,324	860	464	69.6	45.2	24.4	435	509	268			
23	June	23, 1923	10	M.	22.2	Pneumonia	+	37.0	1,667	1,050	617	75.2	47.4	27.8	503	585	362			
24	December	28, 1923	12	M.	30.0	Pneumonia	+	40.5	2,503	1,494	1,019	83.7	49.7	34.0	391	464	284			
25	June	6, 1923	10	F.	27.5	Convalescent	0	37.0	1,980	1,248	732	72.0	45.4	26.6	438	485	360			
26	May	14, 1925	9.5	M.	23.6	Pneumonia	+	38.5	1,523	937	585	64.5	39.7	24.8				8.6	80.5	3.4
27	December	29, 1922	12	M.	31.8	Pneumonia	+	43.0	2,740	1,560	1,180	86.0	49.0	37.0	455	563	312			
28	January	28, 1925	3	M.	12.05	Pneumonia	+	32.8	893	600	293	74.1	49.8	24.3	540	575	469	8.3	49.8	4.1

of pyelitis, three cases of typhoid fever and four miscellaneous febrile patients. The results are given in detail in the accompanying tables. In interpreting the results, the facts brought out in the first paper must be kept in mind. The plasma volume is more constant than the blood volume and is 50 ± 5 milliliters per kilogram of body weight except for children under three years of age when it is about 60 milliliters per kilogram. But the plasma volume in early life, in general, is less constant than in adults. The red cell volume tends to average about 30 milliliters per kilogram of body weight, though considerable variation is found.

The purest examples of a febrile state reported in this paper are the cases of typhoid fever, and the results are consistent in that they all show slightly high plasma volumes during the fever. Case 1 shows 62 and 58 milliliters of plasma per kilogram; case 3, 54 milliliters per kilogram and case 2, 59.5 milliliters during the fever and 40 milliliters during convalescence. It should be noticed that in case 2, there is an actual loss of total plasma from 922 to 654 milliliters and that the change in weight does not account for the change in the proportion of plasma. When it is taken into account that there is a retention of water in fever, the high plasma volumes per kilogram of body weight found in the other typhoid cases indicate definite increase in the total plasma.

The seven cases of pyelitis may be considered examples of less marked and prolonged fever. All show slightly high or normal plasma volume except cases 8 and 9. Case 8 had a low normal plasma volume of 45.7 milliliters per kilogram of body weight and case 9 the definitely low plasma volume of 35.5 milliliters. No other distinction of this case from the others was found except the slightly high concentration of the plasma chlorides.

The miscellaneous group consisting of one patient with thoracic empyema, one with influenza, one with tuberculous meningitis and one with encephalitis shows essentially normal plasma volumes.

The cases of primary pneumonia show rather confusing results especially if one considers only the results obtained on patients on whom a single determination was made during fever. The cases on which determinations were made after, as well as before the crisis, make an interpretation of the results from the former group of patients

possible and for this reason, the latter are tabulated separately. Fourteen isolated observations of the blood volume during lobar pneumonia were made. One would like to relate the plasma volume during fever to the weight just before the illness or at least to the weight after recovery. This might give a correction for the water retained diffusely throughout the body. The magnitude of this imperceptible retention of water was not appreciated at first and for this reason, the blood volumes are compared to the weight during fever. Studying the fourteen cases in this manner, ten show essentially normal plasma volumes, two high and two low plasma volumes. Case 16 shows 51 milliliters per kilogram as compared to a normal for her age of 60 milliliters; case 26, 40 milliliters as compared to the normal of 50 milliliters; cases 17 and 20 show 58 and 59 milliliters respectively as compared to the normal of 50 milliters. However, when one considers that most of the patients with lobar pneumonia take on an appreciable amount of water, it will be seen than in most instances the plasma volumes must have been increased slightly.

The latter point is brought out fairly well in table 2 in which the results during fever and convalescence in the same patient are shown. Patient 29 showed 56 and 51 milliliters per kilogram in two determinations before the crisis and 49 milliliters per kilogram after the crisis. However, there actually was a decrease of about twenty per cent in the plasma volume since the febrile volumes were 894 and 816 milliliters and the afebrile volume 670 milliliters. The loss of weight from 16 to 13.6 kilograms masks the extent of the change when the plasma volume is related to the weight. Case 30 shows little actual change in the plasma volume but due to the loss of weight, the plasma volume increased from 67.5 and 72 milliliters during the fever to 79 milliliters per kilogram during convalescence. This case is unusual in that the plasma and cell volumes are so high under normal conditions. No explanation for this could be found. In case 31, the change in weight from 21.25 to 17.7 kilograms masks the loss of plasma volume from 884 to 820 milliliters, as the plasma volume per kilogram of body weight was 41.6 milliliters during fever and 46 milliliters during convalescence. Case 32 shows a decrease from 880 to 685 milliliters in plasma volume (68 to 56 milliliters per kilogram), and case 33, a decrease from 1,607 to 1,320 milliliters (69 to 59 milliliters per kilogram).

TABLE 2

Case	Date	Age	Sex	Weight	Diagnosis	Fever	Cell volume	Blood volume—total			Blood volume per kilogram of weight			Chloride per 100 ml.			Serum protein		
								Blood	Plasma	Cells	Blood	Plasma	Cells	Blood	Plasma	Cells	Per cent	Grams	Grams per kilogram
		yrs.		*kg.*			*per cent*	*ml.*	*ml.*	*ml.*	*ml.*	*ml.*	*ml.*	*mg.*	*mg.*	*mg.*			
29	January 5, 1923	5	M.	16.0	Pneumonia	+	36.2	1,400	894	507	87.6	55.8	31.7	431	508	296			
29	January 11, 1923	5	M.	16.0	Pneumonia	+	37.2	1,300	816	484	81.3	51.0	30.2	418	518	250			
29	January 19, 1923	5	M.	13.6	Convalescent	0	31.2	975	670	304	71.6	49.2	22.3	484	570	294			
30	November 21, 1923	10	M.	30.0	Pneumonia	+	43.0	3,533	2,016	1,518	118.0	67.5	50.5						
30	November 23, 1923	10	M.	30.0	Pneumonia	+	43.0	3,790	2,160	1,630	126.0	72.0	54.0						
30	December 5, 1923	10	M.	28.4	Convalescent	+	40.0	3,750	2,250	1,500	132.0	79.3	52.8	460	595	258			
31	January 29, 1925	6	M.	21.25	Pneumonia	+	34.6	1,352	884	468	63.6	41.6	22.0		490		8.61	76.1	3.58
31	February 5, 1925	6	M.	17.7	Convalescent	0	38.4	1,330	820	510	75.1	46.3	28.7				7.67	62.9	3.55
32	February 21, 1927	3	M.	12.95	Pneumonia	+	25.9	1,188	880	308	91.8	68.0	23.8		591		7.42	65.3	5.04
32	March 1, 1927	3	M.	12.3	Convalescent	0	30.4	985	685	299	80.0	55.6	24.3				7.63	52.3	4.25
33	February 21, 1927	7	M.	23.3	Pneumonia	+	24.5	2,125	1,607	522	91.4	69.0	22.3		586		6.55	105.0	4.5
33	February 25, 1927	7	M.	22.25	Convalescent	0	22.25	1,869	1,320	548	83.8	59.3	24.6		556		7.85	103.5	4.65
34	February 14, 1927	3.5	M.	14.9	Pneumonia	+	33.0	1,448	970	478	97.3	65.2	32.1		532		7.63	73.0	4.9
34	February 19, 1927	3.5	M.	15.0	Convalescent	0	31.8	1,466	1,000	466	97.8	66.6	31.0				7.42	74.2	4.94
2	May 29, 1923	8	M.	15.5	Typhoid	+	33.0	1,375	922	454	88.8	59.5	29.2	308	449	240			
2	June 15, 1923	8	M.	16.2	Convalescent	0	36.3	1,027	654	373	63.4	40.4	23.0	466	516	377			

Essentially no change is found in case 35. Thus it is seen that there is usually a moderate increase in plasma volume in children with primary pneumonia, but in most cases the imperceptible retention of water is sufficient to mask the increase in plasma volume when the volume during fever is compared to the weight during fever. In four of the six cases studied before and after the crisis, there was an appreciable fall in the absolute plasma volume, after recovery, from the high level found during fever. A higher plasma volume during fever was found also in the only case of typhoid fever studied after recovery.

The chloride concentration of the plasma is a valuable guide to the extent of the physico-chemical changes which have taken place in the pneumonic patients studied. Most of the patients with fever and pneumonia had low plasma chloride concentrations. This would indicate that the physico-chemical changes described in adult lobar pneumonia (14) have taken place in these patients. No relation between the plasma chloride concentration and the plasma volume could be found. It should be noted that the plasma chloride concentration is quite low in the typhoid patient, case 2, and in cases 5, 6 and 8 of pyelitis. There probably is a tendency to low plasma chloride concentration in other fevers beside pneumonia, though sufficient data are not at hand to prove this point.

Chart 1 shows the relation of the plasma and cell chloride concentrations. Part 1 represents the results on the normal children reported in the first paper (15) and Part 2 the results on the febrile patients of this paper. It will be noticed that the cell chloride concentrations in the normal and febrile patients are distributed over the same range of values in both groups—200 to 450 milligrams per 100 milliliters. However, in the febrile groups, the low plasma chloride concentrations tend to be accompanied by low cell chloride concentrations so that there is a tendency of the group to fall along a straight line when represented as in chart 1. There are a number of exceptions so that many cases fall off the line. Evidently though other factors affect the relation of the cell and plasma chlorides, in febrile patients the concentrations of both the cell and plasma chlorides tend to be low.

A satisfactory explanation of the low plasma chloride values found in lobar pneumonia has never been given. Referring to table 2, it will be noticed that the increase in plasma volume is of such a magni-

tude that the additional water could account for the lowering of the concentration of chlorides if we assume no increase in the total chlorides of the body has taken place. Actually there is chloride retention during the febrile stage of pneumonia and release of chlorides after the crisis. Apparently the retention of water in the tissues is great enough to account for not only the retention of chlorides in the body as a whole, but also leads to depletion of the blood chlorides. The lowering of blood chlorides is proably augmented by the increase in plasma volume. In case 29, complete data are given and one can calculate the total chlorides of the blood and plasma. During the fever there were 6 and 5.4 grams of sodium chloride in the blood and

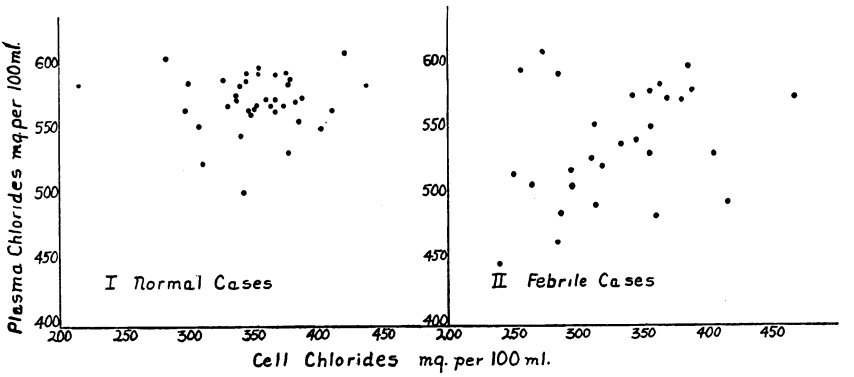

CHART 1. THE RELATION OF THE PLASMA CHLORIDES TO CELL CHLORIDES IN NORMAL CHILDREN AND IN CHILDREN WITH FEVER

4.5 and 4.2 grams of sodium chloride in the plasma; while during convalescence there were 4.8 grams of chloride in the blood and 4.2 grams of chloride in the plasma. Thus the blood dilution is great enough to account for a greater lowering of the chlorides than was actually found. Furthermore, the loss of weight after the crisis in cases 29, 30 and 31 is of such a magnitude that assuming the loss of weight to indicate water retained during fever, one can thereby account for not only the low concentration of plasma chlorides, but also the fact that an increased concentration of chlorides has not been found elsewhere in the body. Cases 32, 33 and 34 did not show the usual loss of weight after the crisis but they also did not show the

usual lowering of the plasma chloride concentration. However, cases 32 and 33 showed the usual drop in plasma volume after the crisis. These facts seem to indicate that the low concentration of plasma chlorides may depend chiefly on the retention of water during fever, and that the plasma volume change is not directly connected with the storage of water.

DISCUSSION

Three factors would seem to be at work in febrile states that might affect the plasma volume. (1) The higher metabolic rate would tend to increase the plasma volume, if the circulation rate remains constant. A higher metabolic rate would tend to make the venous carbon dioxide content show a greater elevation over that of the arterial blood than normal. As pointed out in the first paper of this series, the increased carbon dioxide content of the venous blood over that of the arterial blood, causes a greater increase in the osmotic pressure of the venous blood over that of the arterial blood than normal. This augments the tendency of venous blood to draw water from the tissues and should increase the plasma volume. (2) An increased rate of blood flow would tend to diminish the plasma volume. It is not certain whether there is an increased rate of blood flow in fever. However, in pneumonia and probably in other fevers also, the arterial and venous oxygen saturation becomes more nearly identical and as was pointed out earlier in this paper, this fact can be explained best by a rapid blood circulation. In the first paper of this series, the idea was developed that a rapid circulation would bring the arterial and venous carbon dioxide contents nearer to each other and thereby reduce the difference in osmotic pressure between arterial and venous serum. If the metabolic rate remains constant, this should reduce the amount of circulating fluid. (3) The carbon dioxide absorption curve would be at a lower level due to the higher temperature of the body (Stadie and Martin (16)) and hence the blood would be less efficient as a carbon dioxide and water carrier. From a study of the carbon dioxide absorption curves in other cases together with the blood volumes, minor variations in the carbon dioxide absorption curve seem to exert little or no influence on the plasma volume. However, with greater variations from the normal, changes take place in the plasma volume which may be explained by the changes in the dis-

sociation curve. The level of the curve produces the changes in the plasma volume by altering the differences between venous and arterial carbon dioxide content. If the level of the curve is lower, respirations tend to become more rapid so as to maintain the alkalinity of the blood by blowing off carbon dioxide. Unless the circulation rate is changed, the difference between venous and arterial carbon dioxide content may remain the same. With great lowering of the curve, however, the circulation evidently becomes more rapid, and the venous blood approaches the arterial blood in oxygen and carbon dioxide content as is attested by the reddish appearance of the skin. Under these circumstances, the blood becomes concentrated. This has been observed in diabetic acidosis where the hemoglobin concentration is often very great. Fever alone produces only a slight variation in the carbon dioxide absorption curve and due to this fact, has practically no effect on the blood volume. Nevertheless, certain children and babies react to fever with a severe acidosis due to other factors such as diarrhea, disturbed sugar metabolism leading to acetone body formation, etc., and some of these patients would probably show blood concentration.

In ordinary fever such as studied in this series of cases, the first two factors seem to be the only ones affecting the plasma volume. In a majority of the cases the increased metabolic rate has increased the plasma volume slightly, but this effect is probably diminished in most of the cases by a more rapid circulation and in some instances a rapid circulation may have even diminished the plasma volume.

It should be remarked here that the changes found in this study are all relatively small and, though definite, are within the varying degrees of normality in all but a few instances. The changes are not of such a nature as to suggest any therapeutic measures and are presented largely for their theoretic interest.

SUMMARY

Blood volumes and blood chlorides are reported on febrile children: three with typhoid fever, seven with pyelitis, twenty with primary pneumonia and one each with thoracic empyema, influenza, tuberculous meningitis and encephalitis. In all forty-four, individual observations are reported.

In fever, there is a slight to moderate increase in the plasma volume which is usually accompanied by a proportional increase in the water held diffusely throughout the body. Although the lungs are one of the chief organs of water excretion, the inflammation in primary pneumonia of children does not seem to bring about any changes in the water metabolism which are different from those seen in other fevers.

The data concerning the plasma chlorides in febrile conditions other than pneumonia, though incomplete, suggest that there is a tendency to a low concentration of the plasma chlorides in fever in general. In fever, a lowering of the concentration of the cell chlorides tends to occur when there is a lowering of the concentration of the plasma chlorides.

The retention of water in the plasma and throughout the body during pneumonia is great enough to explain the low chloride concentration of the plasma and the lack of an increased chloride concentration elsewhere in the body and the storage of chlorides during fever.

BIBLIOGRAPHY

1. Leyden, E., Arch. f. klin. Med., 1869, v, 273. Untersuchungen über das Fieber.
2. Lussky, H. O., and Friedstein, H., Am. J. Dis. Child., 1920, xix, 337. Water Retention in Pneumonia.
3. Maver, M. E., and Schwartz, A. B., Arch. Int. Med., 1916, xvii, 459. Studies of Edema in Pneumonia.
4. Hirsch, L., Ztschr. f. Kinderh., 1926, xli, 653. Wasserversuche bei fiebernden Säuglingen.
5. Oppenheimer, S., and Reiss, E., Deutsches Arch. f. klin. Med., 1909, xcvi, 464. Untersuchungen der Blutkonzentrationen bei Scharlach mit besonderer Berücksichtigung der Nephritis.
6. Sandelowsky, J., Deutsches Arch. f. klin. Med., 1909, xcvi, 445. Blutkonzentration bei Pneumonie.
7. Peabody, F. W., J. Exper. Med., 1913, xvii, 71. Studies of the Inorganic Metabolism in Pneumonia with Especial Reference to Calcium and Magnesium.
8. Cook, H. W., Bull. Johns Hopkins Hosp., 1902, xiii, 307. Nitrogen Excretion in Pneumonia, and Its Relation to Resolution.
9. Whipple, G. H., and Cooke, J. V., J. Exper. Med., 1917, xxv, 461. Metabolism of Fasting Dogs Following Proteose Injections.

   Cooke, J. V., and Whipple, G. H., J. Exper. Med., 1918, xxviii, 223. The Metabolism of Dogs with Sterile Abscess, Pancreatitis and Pleuritis.

10. Barbour, H. G., Physiol. Rev., 1921, i, 295. The Heat-regulating Mechanism of the Body.

Barbour, H. G., and Hamilton, W. F., Am. J. Physiol., 1921, lxxiii, 315. Heat Regulation and Water Exchange. VII. Evidence that Cold Anhydremia is Due to Loss of Fluid from the Blood Stream.

Hamilton, W. F., and Barbour, H. G., Am. J. Physiol., 1926, lxxiii, 321. Heat Regulation and Water Exchange. VIII. The Fate of the Fluid Leaving the Blood in Cold Anhydremia.

Barbour, H. G., Loomis, N. M., Frankman, R. W., and Warner, J. H., J. Physiol., 1926, lix, 300. Heat Regulation and Water Exchange. V. The Phase of Blood Dilution in Man.

Hamilton, W. F., Barbour, H. G., and Loomis, N. M., J. Physiol., 1926, lix, 306. Heat Regulation and Water Exchange. VI. The Mobilisation of Water and Salt in Warm Environments.

11. Bancroft, J., Meakins, J. C., Davies, H. W., Duncan-Scott, J. M., and Fetter, W. J., Phil. Proceed. Roy. Soc. of London, 1923, ccxi, 455. On the Relation of External Temperature to Blood Volume.

12. Underhill, F. P., Arch. Int. Med., 1919, xxiii, 753. The Physiology and Experimental Treatment of Poisoning with Lethal War Gases.

13. Underhill, F. P., and Ringer, M., J. Am. Med. Assoc., 1920, lxxv, 1531. Blood Concentration Changes in Influenza.

14. Barach, A. L., Means, J. H., and Woodwell, M. N., J. Biol. Chem., 1922, l, 413. The Hydrogen Ion Concentration and Bicarbonate Level of the Blood in Pneumonia.

Hastings, A. B., Neill, J. M., Morgan, H. J., and Binger, C. A. L., J. Clin. Invest., 1924, i, 25. Blood Reaction and Blood Gases in Pneumonia.

Buckman, T. E., Adams, F. D., Smith, M., and Edwards, H. T., Boston Med. and Surg. J., 1925, cxciii, 997. Chemical Studies of the Blood in Pneumonia.

15. Darrow, D. C., Soule, H. C., and Buckman, T. E., J. Clin. Invest., 1928, v, 243. Blood Volumes in Normal Infants and Children.

16. Stadie, W. C., and Martin, K. A., J. Biol. Chem., 1924, xl, 191. The Thermodynamic Relations of the Oxygen and Base-Combining Properties of Blood.