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Changes in Blood Density in Adult Man in Acute Fever Induced by Typhoid Vaccine and Malaria.

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The experiments herein reported were designed to study the possible changes of blood anhydremia that might be associated with acute paroxysms of fever in adult man. That water plays an important rôle in the regulation of body temperature has long been recognized in both experimental and clinical work. The relationship is, however, a complicated one. Dehydration fevers have been produced experimentally and are recognized clinically. Excessive thirst is a frequent concomitant of fever and the administration of adequate amounts of water is a recognized factor in the treatment of varied types of fever. The details of the regulation mechanism of water distribution, water content and body temperature seem to vary widely in different species of homothermous animals, and in man it may vary with many factors, such as age, body weight, surface area, character of skin covering, etc. With these considerations in mind, it seems obvious that the analysis of the details of the mode of temperature regulation in a given animal species does not necessarily apply to that of a different species of homothermous animal, or even of the same animal at different stages of its life cycle.

Barbour and his associates have presented many cogent contributions suggesting that blood concentration is an essential factor in temperature regulation against cold and that blood dilution is a factor in regulating against heat. His method of measuring the density of the blood reveals these changes in the peripheral blood. From these changes in density he has calculated the volume changes of hydration or dehydration of the blood necessary to produce the density change. To a certain limited extent, therefore, changes in blood density may reflect changes in blood volume. It is obvious to all students of temperature regulation that there are many compensating factors that may mask the relation between blood solids and blood volume; *e. g.*, the addition or withdrawal of erythrocytes to or from the red cell reservoirs, alterations of chloride excretion to maintain chemical composition of hydremic blood, etc. But with all due allowance for these factors, it seems that acute changes of blood hydration can be detected by alterations of blood density.

With these considerations in mind we have studied the changes in blood density before and during the onset of acute fever in adult men induced by the intravenous injection of typhoid vaccine and during the acute chills of malaria. These tests have been made on 4 subjects, all males between the ages of 36 and 45 years. These men were in good physical condition and were being treated for central nervous system lues.

Ten determinations of blood density by Barbour's method[1] were made before and after the injection of typhoid vaccine. In each instance the following standard routine was followed: No breakfast was given, no fluids were taken by mouth after 10 A. M. at which time an adequate dose of typhoid vaccine was injected into the cubital vein. Blood was taken from either the finger tip or from the vein at intervals of 30 minutes to one hour, before the onset of fever, during, and after the fever reaction. All temperatures are oral.

Within 30 minutes after the injection of the vaccine there occurred uniformly an increase in blood density. Uniformly in all determinations the increased change of density precedes the rise of body temperature. Furthermore, the increased density of the blood persists for only a short time and may return to the initial level, even though the body temperature continues to rise. The temperature may remain elevated for several hours after the density has fallen to its original level or lower. (Chart I.)

CHART I.

Four Determinations of Finger Tip Blood Density During Onset of Chill and Fever Induced by Typhoid Vaccine, Given Intravenously. Adult Man.

Time	Body Temp.	Blood Density	Body Temp.	Blood Density	Body Temp.	Blood Density	Body Temp.	Blood Density
10	98.4	1.0586	98.2	1.0530	98.0	1.0530	96.5	1.0548
10:30	98.4	1.0602			98.2	1.0536		
11	98.4	1.0621	98.2	1.0548	98.6	1.0538	96.6	
11:30	101.5	1.0625			100.0	1.0542	96.8	1.0560
12	104.6		99.2	1.0556			97.0	1.0563
12:30	104.0	1.0612			102.2	1.0526		
1			99.8	1.0530			99.5	1.0566
1:30								
2			101.0	1.0532	102.0		99.8	1.0542
2:30	102.0	1.0590						
3					101.6		100.0	
3:30								
4					102.0	1.0528		

In Fig. 1 are shown simultaneous determinations of the density of finger blood and blood from the cubital vein. These determina-

[1] Barbour, H. G., and Hamilton, W. F., *J. Biol. Chem.*, 1926, **69**, 625.

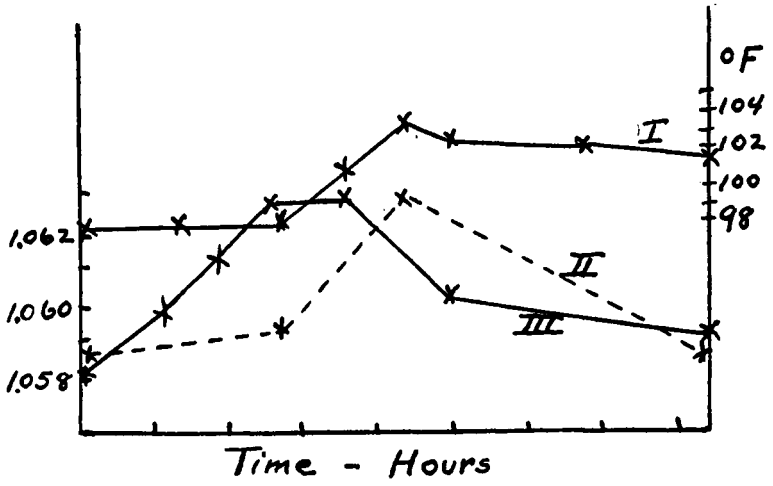

FIG. 1.

Body temperature in °F. shown by curve I. Density of finger tip blood shown by curve III. Density of venous blood by curve II.

tions were made to determine whether or not the density changes were confined to the capillary blood or were also exhibited by venous blood. It will be observed that the same increase in density occurs in the venous blood as in finger tip blood, but it is shortly delayed in time. Routine counts of red blood cells made during the onset of fever showed no significant change. There is a slight lowering of the carbon-dioxide combining power during the chill and onset of fever.

A similar study was made on 2 men preceding, during, and after the chill of malaria (Chart II). In this instance it will be noted that there is an increase in the density of the blood during the chill when the temperature is rising, but when the chill and muscular spasm is over, the blood density falls to a normal level or even below, although the fever is rising and remains elevated for several hours. With the onset of sweating and decline of the fever an increase in blood density may appear.

These findings indicate that in the onset of fever in the adult man, induced by typhoid vaccine or by malaria, there is increased density of the peripheral blood during the preliminary chill when the body temperature begins to rise. This, however, is a short reaction of less than 2 hours' duration. The blood density is then reduced to a normal or subnormal level, although the body temperature may remain elevated for several hours thereafter. It is, therefore, evident that the maintained state of fever induced by

CHART II.
The Changes of Blood Density Associated with the Chill and Fever of Malaria.

Time	Pulse	B.P.	Body Temp.	Blood Density	Comment
		Mr. E. T. B., age 36. CNS Lues. Date 6-16-36			
10 A.M.	68	100/65	98.0	1.0505	Breakfast at 7 A.M. Resting in bed quietly
10:35			98.2		
11	88		98.4		
11:25	86	90/65	98.2	1.0511	1 glass tepid water
12:30	90		98.6	1.0508	
1:05					Chill begins
1:10	140			1.0515	Pallor—chill
1:30	112	115/70	102.0	1.0525	Chill is ending
2	116		104	1.0511	
2:30			104	1.0496	
3					Delirium
4			103.6	1.0499	
5:30			102.0		
		Mr. H. A. M., age 42. CNS Lues. Date 6-25-37.			
9 A.M.	86	95/65	98.0	1.0552	Breakfast at 7 A.M.
11	92	100/70	100.0	1.0549	
3:45 P.M.	106	110/60	103.4	1.0565	Chill—blankets
4:15	120		103.6	1.0543	Water by mouth
5	118		104.0	1.0551	
5:40	120		104.6		Water by mouth
6:15	120		105.0	1.0551	Chill—blankets
8:15	116	105/55	103.8	1.0550	Fruit juice by mouth
10:15	104		100.6	1.0592	Patient is sweating freely
8 A.M.	92		99.0		

these means is not dependent on the concentration, dehydration or anhydremia of the blood itself. If the reduction in blood density is evidence of dilution of the blood, then during the fevered state there is really hydremia of the blood stream which, according to Barbour, is a normal method of reacting to heat.

The study of Soule, Buckman and Darrow[2] on blood volume changes during fever in children indicates that there usually occurs an increase in plasma volume. Our present study on the adult man is in harmony with this conclusion, with the additional finding that in the onset of acute fever with a chill, blood concentration precedes the rise of temperature but this is quickly followed by a lowering of blood density as the fever persists.

Since this work was done we have observed in work done by Black[3] that hay-fever paroxysms induced in a sensitive individual by intranasal injection of ragweed extract is also preceded by a sudden, sharp, but brief, increase in the density of blood taken from the finger. This is apparently due to the vasoconstricting effect of the allergic reaction.

2 Soule, H. C., Buckman, T. E., and Darrow, D. C., *J. Clin. Invest.*, 1928, **5**, 229.
3 Black, J. H., *J. Allergy*, 1936, **8**, 39.

The above findings suggest that the increase in blood density which precedes the acute paroxysm of fever with chill, muscle spasm, pallor and peripheral constriction is probably to be considered as a part of the anaphylactoid reaction of the fever-producing agent rather than an essential factor in the mechanism of fever itself. After the first 2 hours of fever, there is a state of blood dilution. With the termination of the fevered state by sweating, blood concentration may again appear.

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Synthesis of Hippuric Acid in Man Following Intravenous Injection of Sodium Benzoate.

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With the increasing employment of the synthesis of hippuric acid as a means of determining liver function, several disadvantages of this test have been recognized. Vomiting occasionally occurs after the ingestion of sodium benzoate; the collection of urine for 4 hours is at times inconvenient; and in rare instances the condition of the patient may not permit the oral administration of the drug.

To meet these difficulties, the intravenous injection of sodium benzoate was investigated. 1.77 gm. of sodium benzoate (equivalent to 1.5 gm. benzoic acid) dissolved in 20 cc. of distilled water were given intravenously. The subject voided before the test began and a complete urine specimen was collected exactly one hour after the completion of the injection. Approximately 5 minutes were required for the injection. The hippuric acid was determined by the senior author's simple clinical method.[1] The results obtained on normal adult subjects are given in Table I.

From these results one can conclude that after the injection of 1.5 gm. of benzoic acid (as the sodium salt), 0.7 to 0.95 gm. are excreted as hippuric acid during the first hour by a healthy adult subject. If exogenous glycine is supplied, the synthesis of hippuric acid is greatly increased, which indicates that the amount of hippuric acid excreted is a measure of the body's capacity to synthesize glycine.

[1] Quick, A. J., *Am. J. Med. Sci.*, 1933, **185**, 630.