

# CIRCULATION AND RESPIRATION DURING AN EPISODE OF CHILL AND FEVER IN MAN<sup>1</sup>

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Changes in respiratory and circulatory function in patients with fever have been noted by clinicians for many centuries. In recent years a number of investigators have studied respiration and circulation in patients with febrile diseases (1), and many data bearing on these aspects of fever are available. Systematic studies on the reaction of the body to fever in different phases of a febrile reaction, however, have not been published. The present report is based on observations made upon patients experiencing an endogenous febrile reaction, *i.e.*, fever consequent to the introduction of foreign protein or microorganisms into the body. The effects of fever induced by physical means such as heating cabinets, hot baths, infrared radiation and diathermy are discussed elsewhere (1).

## MATERIAL AND METHODS

Studies have been made on 8 subjects ranging in age between 25 and 63 years; 3 of them were women (Cases 1, 3, and 6). All were given fever for therapeutic purposes; the diagnoses included paresis (Case 2), rheumatoid arthritis (Cases 1, 3, 5, 6, 7), gonococcal arthritis (Case 4), and lymphedema of the face of unknown origin (Case 8). Fever was induced by means of the injection intravenously of a typhoid vaccine.

All studies were begun with the patients in the basal state; the patients remained in bed, taking no food and only small amounts of water throughout the period of observation on a given day. All measurements, except that of cardiac output, were made with the patient recumbent in bed; the cardiac output was measured with the patient propped up at an angle of about 30°. The pulse and respiratory rates were counted for 1 minute at frequent intervals. Arterial pressures were measured by the auscultatory method. The cardiac output was measured by the method of Starr and Gamble (2), the oxygen consumption, respiratory minute volume, alveolar air carbon dioxide content and respiratory quotient being determined at the same time. The arm-to-tongue circulation time was measured by means of sodium dehydrocholate (3), and the venous pressure was estimated by the

direct method of Moritz and von Tabora (4). Samples of blood taken from the femoral artery and from femoral and antecubital veins without stasis were analyzed for oxygen and carbon dioxide by means of the method of van Slyke and Neill (5) as modified by Fieser (6). The lung volume and its subdivisions were measured by the method of Christie (7), modified somewhat (8), the oxygen consumption being estimated at the same time. The method of Gibson and Evelyn (9) was used for measuring the plasma and blood volumes; the "direct" technique, using repeated injections of dye, and the "indirect" technique, using repeated observations after a single injection, were both employed. An attempt to study the function of lymphatics was made by means of a method suggested by Griffith (10), using the dye T-1824. The small blood vessels of the nailfold were studied by means of a microscope which magnified 100 times after cleansing the skin with xylol and application of liquid petrolatum to the area to be observed. The pH of the arterial blood was studied by means of a potentiometer with glass electrodes.

## OBSERVATIONS

1. *Clinical findings.* A febrile episode was found to consist of 4 phases which have been designated: (1) *prodrome*, (2) *chill*, (3) *flush*, and (4) *defervescence*.

The *prodrome* began after the injection of the typhoid vaccine, lasted for 30 to 90 minutes and was characterized by a variety of complaints including lassitude, headache, aches and pains, and malaise. The *chill* phase developed rapidly and manifested itself by increasing pallor, greyish cyanosis, narrowing of all the superficial veins, hyperventilation, the appearance of a few beads of perspiration on the face and, at times, gooseflesh over the extremities also. Nausea occurred in almost all patients and was associated with vomiting in some. The rectal temperature rose, but the skin remained cool; the patients complained of feeling cold and exhibited a strong tendency to shiver. In some experiments this tendency manifested itself only by tensing of the muscles, while in others vigorous rigors occurred. If rigors developed, they could be abated by cov-

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ering the patient, and if not present, they could be precipitated by exposing the patient to a blast of cool air or by placing a small piece of ice in his hand. Urine formation was minimal or absent during the *chill* phase. The *chill* phase lasted for

approximately an hour and one-half. It could be prevented by the previous administration of antipyretic drugs. The *flush* phase was characterized by the rapid development of a generalized flush which usually persisted but which might regress

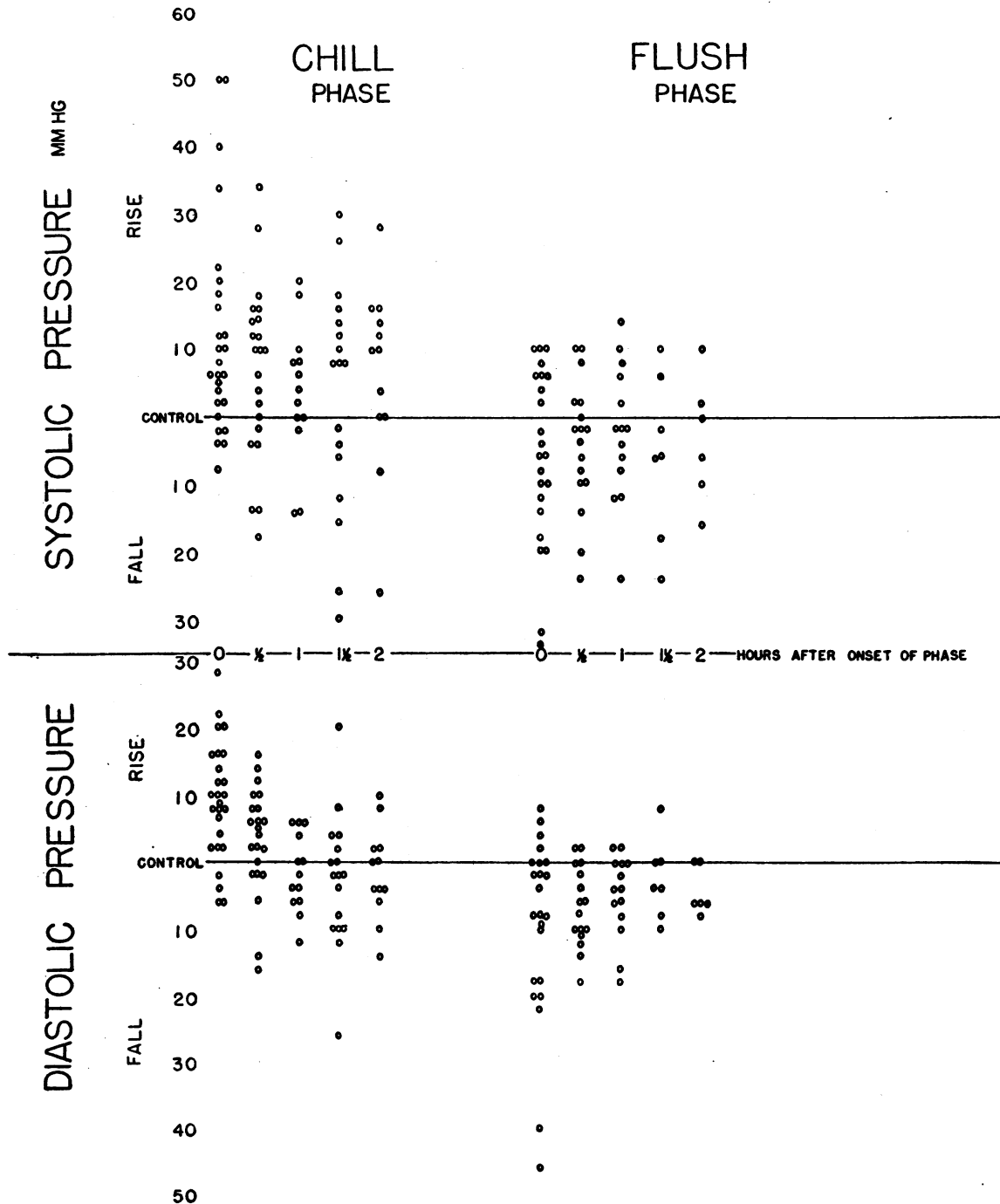


FIG. 1. CHANGES IN BLOOD PRESSURE IN ALL STUDIES DURING A FEBRILE REACTION

somewhat initially before becoming established. The cutaneous veins became greatly dilated. A drenching sweat often developed at or shortly after the appearance of the cutaneous flush, but in patients who had had a severe *chill* reaction the onset of severe sweating was often delayed for 10 to 20 minutes. At about the time of the establishment of the *flush* phase the patient complained of feeling warm and the skin felt hot; the rectal temperature remained at a high level with only minor fluctuations. A pounding headache was usually present. Nausea and vomiting were relieved with the onset of the *flush* phase. The onset of the *flush* phase was often associated with a diuresis. The *flush* phase lasted for approximately an hour and then passed gradually into the phase of *defervescence* when all abnormal findings regressed over a period of several hours. In a few instances, *defervescence* was interrupted by a second *chill* phase which instituted another typical febrile cycle.

2. *Cutaneous capillary microscopy.* No changes in cutaneous circulation occurred during the *prodrome*. The *chill* phase was ushered in by the rapid disappearance of most of the capillaries, the few remaining visible capillaries becoming greatly narrowed and containing blood moving abnormally slowly. The columns of blood in the capillaries appeared segmented. The vasoconstriction in some instances was at first variable, but soon became

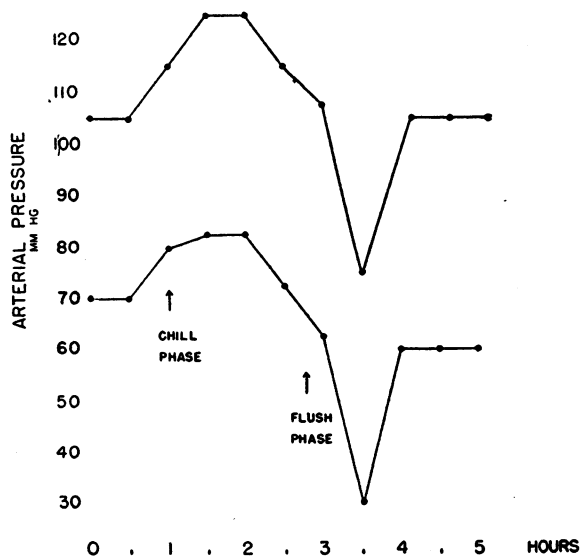


FIG. 2. INITIAL RISE IN ARTERIAL PRESSURE IN *Chill* PHASE AND MARKED FALL IN *Flush* PHASE

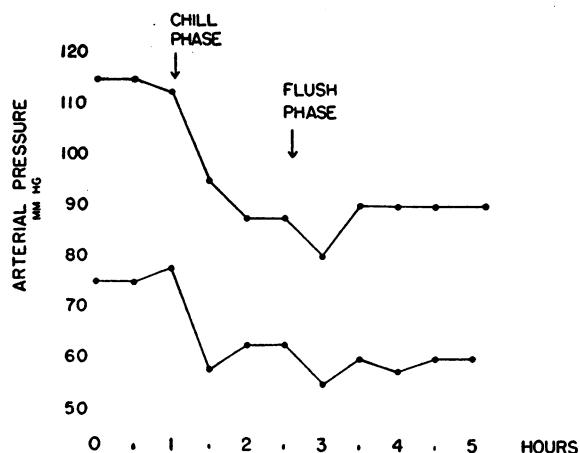


FIG. 3. FALL IN ARTERIAL PRESSURE IN *Chill* PHASE AND FURTHER DECREASE IN *Flush* PHASE

marked. In all instances it persisted until the onset of the *flush* phase. The latter was associated with the rapid appearance of large numbers of widely open capillaries containing blood moving very rapidly. All visible vessels, including arterioles and venules, appeared to pulsate. In some instances the onset of the *flush* phase was associated with the alternate appearance and regression of vasodilatation for a few minutes until finally the vasodilatation became established. *Defervescence* was characterized by a gradual return toward normal.

3. *Arterial pressure.* No changes occurred during the *prodrome*. A rise in systolic and diastolic blood pressure usually occurred in the early part of the *chill* phase, but this rise was not noted in 5 of 26 studies on the arterial pressure. In 7 experiments the arterial pressure fell below the control level late in the *chill* phase, the maximal decreases being 30 mm. Hg systolic and 26 mm. Hg diastolic. The onset of the *flush* phase was associated with a fall in arterial pressure, the maximal decrease below the control levels being 34 mm. Hg systolic and 46 mm. Hg diastolic. The arterial pressure gradually returned to normal during *defervescence* (Figures 1 to 3).

4. *Venous pressure.* No striking changes occurred, but a tendency toward lowering of the venous pressure became apparent during the *chill* phase (Table I), with resumption of normal levels during the *flush* phase.

5. *Cardiac output and arteriovenous oxygen difference.* The minute volume output of the

TABLE I  
Venous pressure

Case	Venous pressure	Remarks	Rectal temperature
	cm. of H <sub>2</sub> O		° F.
1	2.9	Control	99.2
	2.9	Early chill	99.6
	5.9	Moderate chill	101.3
	2.1	Moderate flush	102.0
2	9.3	Control	99.4
	3.3	Early chill	100.1
	3.1	Moderate chill	100.9
	3.5	Moderate flush	104.2
3	6.5	Control	99.3
	6.0	Early chill	101.7
	1.5	Severe chill	104.6
	2.5	Moderate flush	105.2
4	3.0	Control	99.3
	3.9	Moderate chill	103.3
	3.5	Moderate flush	105.7
	2.0	Defervescence	105.5
5	4.5	Control	99.0
	1.5	Severe chill	99.8
	3.5	Moderate chill	103.4
7	1.5	Control	99.1
	0.5	Moderate chill	101.5
	1.0	Moderate flush	103.5
8	4.7	Control	99.1
	2.0	Early chill	100.5
	1.8	Severe chill	101.2
	5.0	Moderate flush	103.5

heart and arteriovenous oxygen difference were normal before the onset of the *chill* phase in all 6 subjects studied (Table II). Changes in cardiac output were variable during the *chill* phase, increases occurring in half the cases. However, the increases in cardiac output which occurred were, except in 1 experiment, smaller than expected from the observed changes in oxygen consumption; in 2 of the 3 patients the cardiac output relative to oxygen consumption fell 14 and 15 per cent. In the patients in whom cardiac output did not rise at any time and fell only in the *chill* phase, the absolute decreases were between 12 and 33 per cent, and the decreases relative to oxygen consumption between 24 and 57 per cent. In the *chill* phase a variable increase in arteriovenous oxygen difference occurred, ranging from 1 to 131 per cent of the control value. In 5 of the 6 patients the arteriovenous difference increased by 16 per cent or more and in 1 instance a fall occurred. The amount of increase in arteriovenous difference varied roughly with the severity of the *chill* reaction. In the *flush* phase all pa-

tients exhibited an increase in cardiac output in excess of the rise in oxygen consumption; the absolute increase was between 45 and 182 per cent of the control value and the increase relative to oxygen consumption was between 10 and 86 per cent. The arteriovenous oxygen difference fell in all experiments by 9 to 46 per cent. The changes during the *flush* phase paralleled roughly the clinical manifestations of the reaction.

6. *Circulation time.* Slowing of the arm-to-tongue time occurred during the *chill* phase in 3 of the 4 patients studied (Table II). The slowing varied roughly with the severity of the *chill* reaction and ranged between 2 and 13 seconds, or 11 to 100 per cent, of the control level. In 1 of these the circulation time became accelerated somewhat late in the *chill* phase. The fourth subject showed an acceleration of 3 seconds, or 16 per cent, when studied in the *chill* phase. During the *flush* phase the circulation times became accelerated in all instances by 6 to 8.5 seconds, or 28 to 45 per cent of the control value. The changes during the *chill* and *flush* phases varied roughly with the severity of the reactions as judged by clinical criteria.

7. *Pulse rate.* A roughly linear relation existed between rectal temperature and pulse rate (Figure 4). The average rise was approximately 10 beats per degree of fever.

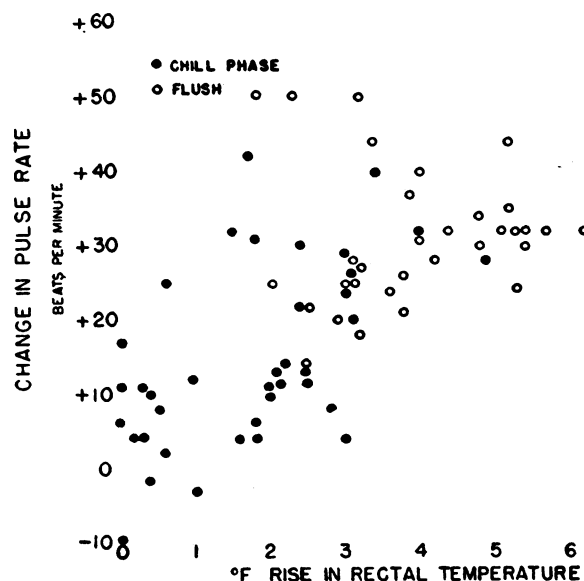


FIG. 4. CHANGES IN PULSE RATE DURING A FEBRILE REACTION

TABLE II  
*Cardiac output and circulation time*

Case	Cardiac output		Arteriovenous oxygen difference  <i>volumes per cent</i>	Circulation time  <i>seconds</i>	Remarks	Rectal temperature  <i>° F.</i>
	<i>L. per minute</i>	<i>L. per 100 ml. of O<sub>2</sub> consumed</i>				
1	3.98	1.74	5.77	18	Control	98.9
	3.95	1.72	5.80	20	Early mild chill	99.6
	4.41	1.82	5.49	14	Late mild chill	101.9
	5.78	2.29	4.36	12	Moderate flush	102.8
	5.05	1.90	5.24	14	Defervescence	102.0
3	3.66	1.81	5.52	13	Control	99.3
	2.74	1.21	8.25	26	Moderate chill	102.5
	5.88	2.20	4.54		Moderate flush	104.0
4	4.46	1.66	6.02	19.5	Control	99.3
	3.92	1.27	7.84	25	Moderate chill	103.6
	2.89	0.72	13.93	31	Severe chill	105.6
	12.58	3.09	3.21	14	Severe flush	104.2
6	3.54	1.73	5.73		Control	98.0
	3.92	1.47	6.79		Mild chill	102.0
	6.90	2.34	4.26		Moderate flush	104.3
7	3.81	1.58	6.33		Control	98.7
	3.07	1.00	9.81		Severe chill	103.3
	6.78	2.10	4.75		Moderate flush	103.8
8	5.15	2.13	4.71	19	Control	98.7
	5.45	1.83	5.47	16	Mild chill	102.0
	8.01	2.34	4.28	10.5	Moderate flush	103.7

8. *Oxygen consumption.* In the absence of rigors or muscle tensing in the patients, the oxygen consumption varied roughly with the rectal temperature (Figure 5). The average rise in oxygen

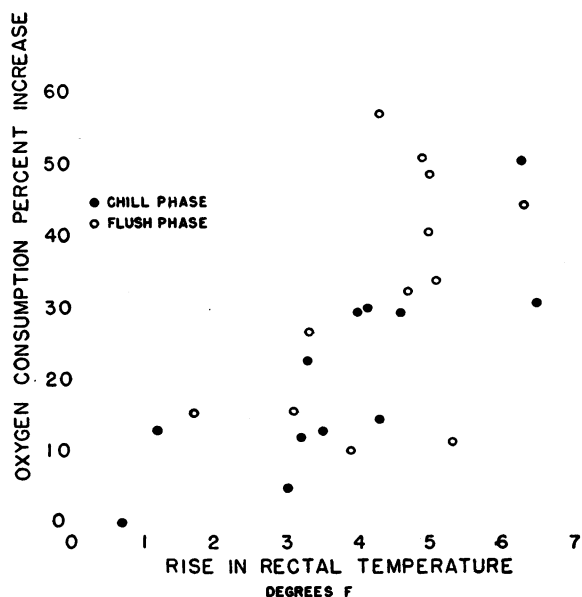


FIG. 5. INCREASE IN OXYGEN CONSUMPTION DURING A FEBRILE REACTION

consumption was approximately 7 per cent per degree of fever.

9. *Respiratory minute volume.* The respiratory minute volume rose during both the *chill* and *flush* phases (Table III). During the *chill* phase the hyperventilation exceeded the rise in oxygen consumption, while during the *flush* phase the respiratory volume relative to oxygen consumption per minute fell to or toward normal.

10. *Respiratory rate and tidal air.* The respiratory rate increased somewhat more than the minute volume during the *chill* phase, so that the tidal air fell slightly (Table III). During the *flush* phase the rate of respiration fell relative to the respiratory minute volume, and the tidal air volume rose to or somewhat above normal in all instances but 1 (Case 6).

11. *Respiratory quotient.* The respiratory quotient was between 0.78 and 0.83 before the body temperature rose. It was between 0.80 and 1.03 in the *chill* phase and between 0.81 and 0.86 in the *flush* phase.

12. *Alveolar air carbon dioxide content.* The alveolar air carbon dioxide content was between 5.0 and 5.6 per cent in the control and *prodromal*

periods (Table III). It fell to 3.9 to 5.2 per cent in the *chill* and was between 4.7 and 4.9 per cent in the *flush* phase.

13. *Subdivisions of the lung volume.* The functional residual (subtidal) air was increased by 2

to 24 per cent in the *chill* phase, the average increase being 12 per cent; in only 2 patients was the increase larger than the error of the method (Table IV). In the *flush* phase and *defervescence* the increases were between 1 and 16 per cent and

TABLE III  
*Respiratory dynamics*

Case	Respiratory rate	Tidal air	Respiratory volume		Alveolar CO <sub>2</sub>	Remarks	Rectal temperature
	<i>per minute</i>	<i>ml.</i>	<i>L. per minute</i>	<i>L. per 100 ml. of O<sub>2</sub> consumed</i>	<i>per cent</i>		<i>° F.</i>
1	13	414	5.38	2.35	5.3	Control	98.9
	17	325	5.52	2.41	5.2	Early mild chill	99.6
	23	317	7.29	3.01	4.7	Mild chill	101.9
	18	400	7.20	2.86	4.6	Moderate flush	102.8
	15.5	427	6.62	2.50	4.6	Defervescence	102.0
3	16	328	5.25	2.60	5.5	Control	99.3
	21	309	6.50	2.88	5.0	Moderate chill	102.5
	19	349	6.63	2.47	4.9	Moderate flush	104.0
4	12	635	7.62	2.84	5.0	Control	99.3
	18.5	491	9.09	2.96	4.2	Moderate chill	103.6
	18	520	9.37	2.32	4.3	Severe chill	105.6
	16.5	683	11.27	2.79	4.3	Severe flush	104.2
6	10	457	4.57	2.23	5.6	Control	98.0
	25	261	6.51	2.45	4.6	Mild chill	102.0
	19	343	6.51	2.22	4.8	Moderate flush	104.3
7	13	525	6.81	2.83	5.5	Control	98.7
	23	518	12.41	3.97	3.9	Severe chill	103.3
	19	624	11.56	3.59	4.1	Moderate flush	103.8
8	12.5	516	6.45	2.65	5.1	Control	98.7
	17	505	9.09	3.05	4.2	Mild chill	102.0
	16	578	9.25	2.70	4.5	Moderate flush	103.7

TABLE IV  
*Subdivisions of the lung volume*

Case	Functional residual air	Residual air	Reserve air	Complemental air	Vital capacity	Total capacity	Phase	Rectal temperature
	<i>ml.</i>	<i>ml.</i>	<i>ml.</i>	<i>ml.</i>	<i>ml.</i>	<i>ml.</i>		<i>° F.</i>
1	1935	1320	615	2955	3570	4890	Control	98.9
	1965	1330	635	2800	3435	4765	Slight chill	100.0
	2005	1310	695	2935	3630	4940	Moderate flush	102.2
	1960	1285	675	2935	3610	4895	Defervescence	100.5
3	2330	1895	435	1390	1825	3720	Control	99.3
	2420	2125	295	1490	1500	3910	Severe chill	104.0
4	2535	1545	990	4365	5355	6900	Slight flush	103.6
	2885	2070	815	3690	4505	6775	Control	99.1
	2790	1820	970	4325	5295	7115	Severe chill	105.6
7	2610	2255	355	3250	3605	5860	Severe flush	104.4
	2795	2555	240	3055	3295	5850	Control	99.1
	2675	2300	375	3250	3625	5925	Severe chill	102.6
8	1885	1230	655	3560	4215	5445	Moderate flush	103.4
	2340	1785	555	3010	3565	5350	Control	99.8
	2180	1485	695	3410	4105	5590	Moderate chill	103.9

TABLE V  
Blood oxygen and carbon dioxide content

Case	Arterial blood			Venous blood		Rectal temperature	Remarks
	Oxygen content	Oxygen saturation	Carbon dioxide content	Oxygen content	Carbon dioxide content		
	<i>per cent</i>	<i>per cent</i>	<i>per cent</i>	<i>per cent</i>	<i>per cent</i>	<i>° F.</i>	
1	15.23	100	44.68	11.48	47.39	99.7	Control
				9.92	46.45	100.5	Early chill
				5.93	39.09	102.0	Moderate chill
	15.43	94	40.52			102.4	Moderate chill
				14.79	41.78	103.4	Moderate flush
	15.29	99	41.11			104.5	Moderate flush
				13.59	42.72		Defervescence
2	18.32	94	43.43	12.72*	48.68	99.0	Control
	19.80	100	41.25	7.32*	49.23	100.1	Early chill
	19.07	98	40.01	9.97*	48.25	102.7	Moderate chill
				16.92	41.08	104.2	Moderate flush
3	19.96	94	41.30	14.64	42.55	99.6	Control
				4.89	46.90	101.1	Severe chill
	20.32	96	33.50			103.6	Severe chill
				15.70	36.32	104.7	Moderate flush
				16.93	39.00	103.7	Defervescence
4	18.63	90	42.95	10.23	49.41	99.2	Control
				4.10	49.60	102.5	Severe chill
	18.25	88	35.06	9.51	46.25	104.8	Early flush
				13.31	44.84	104.1	Severe flush
5	20.14	93	46.54	15.23	50.55	98.6	Control
	20.00	93	40.65	8.07	47.16	101.6	Severe chill
	19.20	89	40.88	17.65	44.43	105.0	Moderate flush
6	16.54	94	56.04	10.65	60.95	98.0	Control
				9.88	55.85	102.0	Mild chill
	15.06	86	50.87	12.14	54.87	102.6	Moderate flush
7				13.55	47.08	98.3	Control
				6.34	49.49	99.1	Early severe chill
				9.33	47.08	101.4	Severe chill
				8.94*	46.30	101.4	Severe chill
				9.25	44.30	103.7	Severe chill
				15.47	40.78	104.1	Moderate flush
				12.38*	44.15	102.1	Defervescence

\* Femoral venous blood.

averaged 7 per cent. The volume of the residual air was somewhat increased during the febrile reaction in 4 of the 5 patients studied. During the *chill* phase the increases ranged between 1 and 45 per cent of the original values and averaged 23 per cent. It was outside the range of error of the method in all cases but one. During the *flush* phase the changes ranged between minus 3 and plus 21 per cent, averaging plus 10 per cent. The reserve (supplemental) air fell in 4 patients, the decreases ranging between 15 and 32 per cent in the *chill* phase and rose 13 per cent in 1 case. The average change was minus 13 per cent. In the *flush* phase no consistent change occurred. The complemental air was also diminished by 5 to 15

per cent, averaging 10 per cent, in the *chill* and showed no consistent change in the *flush* phase. The decreases in vital capacity were 0 to 18 per cent, averaging 11 per cent, in the *chill* phase; no consistent change occurred in the *flush* phase. The total lung volume showed no significant change at any time.

14. *Arterial blood gases.* Striking changes in arterial blood oxygen concentration did not occur in the patients studied; slight decreases in saturation were found in 2 who hyperventilated markedly (Table V). The arterial blood carbon dioxide concentration showed a considerable fall during the *chill* with little or no further change in the *flush* phase.

15. *Venous blood gases.* During the *chill* phase a fall in venous blood oxygen content, ranging between 0.77 and 9.71 volumes per cent, was observed; the amount of fall appeared to vary with the severity of the chill reaction (Table V). In the *flush* phase the venous blood oxygen content rose to levels 1.49 to 4.20 volumes per cent above the control values and approached the concentrations found in the arterial blood. The venous blood carbon dioxide content was variable during the *chill* phase, but fell in the *flush* phase by 3.16 to 7.60 volumes per cent below the control values. A return toward normal occurred during *defervescence*.

16. *Arterial pH.* Changes in the direction of alkalosis occurred in all patients studied (Table

TABLE VI  
*Arterial blood pH*

Case	pH	Remarks	Rectal temperature
4	7.35	Control	° F. 99.3
	7.42	Chill	101.3
	7.44	Flush	104.7
	7.39	Defervescence	103.7
5	7.33	Control	98.6
	7.44	Chill	102.2
7	7.50	Control	99.6
	7.60	Early chill	100.7
	7.65	Late chill	103.0

TABLE VII  
*Measurements of hematocrit and plasma volume*

Case	Hemato- crit	Plasma volume	Remarks	Rectal tem- perature
1	percentage of cells	ml.		° F.
	45	2800	Control	100.0
	45	2820	Early chill	100.5
	45	2800	Moderate chill	102.8
4	45	2950	Moderate flush	103.5
	42	3475	Control	99.4
	42	3475	Prodrome	99.4
	43	3395	Early chill	102.4
5	44	3175	Moderate chill	102.9
	43	3210	Severe flush	105.5
	43	3560	Defervescence	103.4
8	38	4310	Control	98.6
	39.5	4300	Prodrome	98.6
	41	4170	Moderate chill	103.0
	39	4195	Moderate flush	103.9
8	41	2810	Control	99.1
	40.5	2910	Severe chill	102.0

TABLE VIII  
*Lymphatic function*

Case	Area stained		Time	Streamers	Remarks	Rectal tem- pera- ture
	Initial	Final				
7	mm.	mm.	minutes			° F.
	5×5	6×6	20	0	Control	99.4
	6×6	6×8	20	0	Prodrome	99.4
	5×5	7×7	20	0	Chill	100.8
	2×3	7×6	3	++++	Flush	102.4
8	5×5	6×6	20	0	Control	98.7
	5×4	5×6	20	0	Chill	102.0
	5×4	8×7	4	++++	Flush	103.5

VI). During the *chill* phase and in the absence of rigors, the pH rose 0.07 to 0.15. In the *flush* phase it was still elevated and fell during *defervescence*.

17. *Blood volume.* No changes in plasma volume or hematocrit occurred during the febrile episode (Table VII).

18. *Lymphatic function.* Wheals on the forearm containing the blue dye increased in size by 75 to 100 per cent slowly during a 20-minute period during the control period (Table VIII). Wheals made during the *chill* phase increased by the same amount or a little less. During the *flush* phase, however, a great increase in the size of the wheal occurred within 3 to 5 minutes; streamers radiating out from the wheal also became visible.

## DISCUSSION

The clinical features of the various phases of a febrile reaction have long been recognized in a variety of infectious processes. Patients in whom a foreign protein has been injected pass through the entire course of the febrile reaction within a period of hours, so that comparative studies during the various phases may be made readily and with a minimum of variation consequent to uncontrolled extraneous factors. The endogenous febrile reaction studied under these circumstances gives rise to a series of clinical and physiological changes which occur in regular sequence and fall into uniform patterns.

The significance of the *prodromal* period is not clear, nor are the mechanisms which act during it clearly understood. This phase is characterized by such non-specific complaints as headache, malaise, and lassitude; detectable changes in car-



diovascular and respiratory dynamics do not occur. It is terminated by the onset of marked generalized vasoconstriction which is evident in the skin and assumed elsewhere because of the observed changes in arterial blood pressure. The narrowing or disappearance of cutaneous capillaries and the sluggish cutaneous flow observed here, and previously by others, was ascribed to marked arteriolar constriction (11, 12, 13). The conclusion that capillary blood pressure is unchanged during the *chill* phase of malaria (14) cannot be accepted because of the fact that the indirect method used is inaccurate. The elevation of arterial blood pressure which occurred in some of the experiments of the present study, as well as in those of other authors (14 to 17), indicates that arteriolar narrowing is widespread. More marked and persistent increases in arterial blood pressure would probably develop if it were not for the occurrence of changes in cardiac output which tend to lower arterial pressure. Not only are capillaries and arterial vessels constricted, but the visible veins also become markedly narrowed. It appears, therefore, that the vasoconstriction is a widespread phenomenon involving all vascular elements. On the other hand, some areas within the body probably do not participate in the fairly generalized vasoconstriction and indeed may be the seat of vasodilatation, for the circulating blood volume shows no change as measured here and as previously described (18). Studies on visceral circulation in an endogenous febrile reaction are scanty. A decrease in the size of the kidneys has been described (19) in animals in which a febrile reaction was induced, so that these organs are probably the site of vasoconstriction. Other authors have found a decrease in cerebral (20) and in renal (16) flow in the *chill* phase of induced febrile reactions. On the other hand, the findings of the present study which show an increase in the residual air volume and in the ratio of residual air volume to total pulmonary capacity in the *chill* phase suggest that some degree of pulmonary congestion may occur.

During the *chill* phase the cardiac output fell in some experiments and in the rest failed to rise in proportion to the increase in metabolic rate which occurred as the body temperature rose. This phenomenon was paralleled by increases in arteriovenous oxygen difference and by decreased oxygen

content of venous blood taken from the antecubital or femoral veins. None of the findings suggested direct depression of cardiac function as the cause of the observed absolute or relative decrease in minute volume output, *i.e.*, bradycardia did not occur and the venous pressure did not rise. The tachycardia likewise did not reach levels which might cause lowering of the cardiac output. It is probable that the changes in cardiac output which occurred in the *chill* phase in the patients studied were the resultant of 2 opposing forces: (1) a tendency to increase parallel with the rising metabolic rate associated with fever; and (2) a tendency to decrease as a consequence of impairment of venous return due to intense vasoconstriction. In regard to the latter, it is of interest that the venous pressure tended to fall somewhat during the *chill* phase. One worker (14) had found no change in venous pressure during the *chill* phase of a malarial paroxysm. The arm-to-tongue circulation time was slowed early in the *chill* phase in every patient. Late in this phase, the circulation time in some patients became somewhat accelerated, while in others it remained slow. The initial slowing was probably consequent largely or entirely to slow flow secondary to cutaneous vasoconstriction, for cooling the skin has been shown to slow the arm-to-tongue time (21). During the early part of the *chill* phase changes in cardiac output are probably minimal or absent. Later in this period, however, the cardiac output may fall and when it does so, the circulation time becomes more prolonged. It is not possible to state how much of the prolongation in such instances is the effect of cutaneous vasoconstriction in the arm *per se* and how much is the consequence of diminished cardiac output.

Changes in respiration during the *chill* phase consist in increased respiratory minute volumes greatly in excess of increases in oxygen consumption due to the fever. There were also exaggerated increases in respiratory rate which resulted in slight or moderate decreases in tidal air volume. Several mechanisms may be responsible for the excessive hyperventilation of the *chill* phase. The above-described cutaneous vasoconstriction limits heat dispersal *via* the skin (22, 23), so that the effects of increased heat production are exaggerated and the body temperature rises rapidly. Increased temperatures within the brain give rise

to hyperventilation (24 to 27), presumably in an attempt to lower body temperature. Another factor which may increase respiratory minute volume out of proportion to metabolic requirements is the stasis which occurs when the cardiac output falls or at least fails to rise in proportion to oxygen consumption. Some degree of tissue anoxia is present in all such instances and in some experiments a rise in venous blood carbon dioxide also occurred. A third mechanism favoring excessive hyperventilation might be reflexes activated by pulmonary congestion. The importance of each of these causative factors cannot be evaluated. The respiratory changes which occurred in the *chill* phase resulted in a lowering of alveolar air carbon dioxide content and blowing off of appreciable amounts of carbon dioxide from the blood. The arterial blood carbon dioxide was significantly lowered, while the changes in the venous blood were the resultant of 2 opposing factors: (1) lowering of blood carbon dioxide consequent to hyperventilation; and (2) elevation of blood carbon dioxide consequent to stasis. Studies of respiratory quotient showed a tendency toward the giving off of larger amounts of carbon dioxide than in the basal state, but this was not definitely consequent solely to hyperventilation, since increased metabolism of carbohydrate also occurs. The loss of carbon dioxide from the blood gave rise to a tendency toward alkalosis; that alkalosis was not more marked is probably a consequence of the elevation of blood lactate and pyruvate levels which occurs in fever (28).

The marked generalized vasodilatation which characterized the *flush* phase presumably involved all vascular elements. Microscopy revealed the capillaries of the skin to be markedly increased in number and size and direct inspection showed the superficial veins to be dilated. Arteriolar dilatation probably also was present, for some fall in arterial blood pressure and the appearance of capillary dilatation occurred regularly. In addition, arteriovenous shunts probably became patent, for venous blood became arterialized, often markedly so. The slight rise in venous pressure which was noted might also have been consequent to opening of arteriovenous channels. Nevertheless, vascular constriction must have occurred somewhere in the body, for the circulating blood volume was unchanged. Increases in cardiac output

in the *flush* phase were out of proportion to the metabolic needs, and the arm-to-tongue time was greatly accelerated. The renal flow may also increase in the *flush* phase (16, 19, 30). These phenomena may have been consequent, at least in part, to increased venous return secondary to opening of the arteriovenous shunts. Another factor making for this increase in cardiac output is elevated cerebral temperature (25). The absence of stasis in the *flush* phase and the restoration of 1 of the mechanisms for heat dispersal lost in the *chill* phase, *i.e.*, increased circulation through the skin, removes 2 factors which exaggerate the hyperventilation of the *chill* phase. Diminished pulmonary congestion has the same effect. Accordingly, the respiratory minute volume is lowered relative to oxygen consumption and returns to or toward a normal relation with metabolic rate. Loss of carbon dioxide from the arterial blood and alkalosis, therefore, do not progress.

A state which had the clinical characteristics of shock developed in patients in whom the severest *chill* reactions occurred. The patients were pale, cold, sweaty, anxious, and dyspneic; they showed tachycardia and a falling arterial blood pressure. Physiological studies made at this time revealed very low cardiac output, marked deoxygenation of venous blood, and a fall in venous pressure. This state differed from that seen in other types of shock in that blood volume, oxygen consumption, and rectal temperature did not fall; the syndrome was, in addition, self-limited. The clinical manifestations of shock were in some experiments temporarily exaggerated at the onset of the *flush* phase when vasodilatation rapidly developed.

The observations on lymphatic function made here are difficult to interpret. It appears that lymphatic flow is increased in the *flush* phase of the febrile reaction, but the mechanisms responsible for this change are difficult to evaluate. Vasodilatation and elevated capillary pressure tend to increase filtration from the blood. The former obviously occurs and the latter may also. A rise in capillary pressure when the skin is heated locally has been demonstrated (31). Whether such a rise can also occur in a febrile reaction when vasodilatation is generalized and may be extreme cannot be determined.

The factors which initiate the febrile reaction and determine its phases are not clearly understood. The cause of the increased heat production which occurs in a febrile reaction is probably related in some way to hypothalamic function, for damage to that area prevents it (32). Similarly, the vasomotor manifestations of the febrile reaction appear to be initiated by the hypothalamus. The onset of flushing and sweating occurs at a higher level in patients undergoing a febrile reaction than in subjects exposed to warm environmental temperatures and, accordingly, it appears that thermostatic control of the peripheral vascular and sweating mechanisms is reset at a higher than normal level in endogenous fever.

#### SUMMARY AND CONCLUSIONS

1. Changes in circulation and respiration have been studied in 8 patients following the injection intravenously of typhoid vaccine.

2. The febrile reaction consisted of 4 phases: (a) *prodrome*, (b) *chill*, (c) *flush*, (d) *defervescence*. Each had distinctive clinical features and, except for the prodrome, each was characterized by a definite series of physiological phenomena.

3. The *chill* phase was characterized by intense vasoconstriction, decreased cardiac output, slowed circulation time, hyperventilation, alkalosis, and oliguria. There was an initial hypertension followed by hypotension and, in some experiments, the development of shock.

4. The *flush* phase was characterized by marked vasodilatation, drenching sweats, increased cardiac output, accelerated circulation time, a lesser degree of hyperventilation, maintained alkalosis, diuresis, and in many experiments a sudden fall in blood pressure at the onset of the phase.

5. *Defervescence* was characterized by a return of all mechanisms toward normal.

6. Lymphatic function was apparently increased in the *flush* phase.

7. No change in circulating plasma volume occurred during any phase of the febrile reaction.

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