CLINICAL CALORIMETRY XXXII

TEMPERATURE REGULATION AFTER THE INTRAVENOUS INJECTION OF PROTEOSE AND TYPHOID VACCINE *

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During the last seven or eight years, many clinicians have been treating arthritic patients by means of intravenous injections of foreign protein. These produce chills which resemble malarial paroxysms and afford an ideal opportunity for studying in man the phenomena of temperature regulation. In 1917 the chills and fever in several cases of malaria were studied in the Sage calorimeter.¹ The present investigation was undertaken as a supplement to the work in malaria in order to study in more detail the mechanism of the rise and fall of body temperature.

The gaseous exchanges of patients have been studied by Kraus and Chvostek² after giving tuberculin, and in animals by Freund and Grafe,³ Versar, who gave infusions of sodium chlorid,⁴ and by Berrar,⁵ who used aloin. In general, these animal experiments showed a rise in total oxidative processes accompanying the rise in temperature. Sometimes this increase amounted to 130 per cent.

The other phenomena which follow the intravenous injection of foreign protein have been studied in many clinics since the therapeutic application of this procedure was developed by Ichikawa, Kraus, Jobling and Petersen and others. Miller and Lusk⁶ reported favorable results in arthritis and many others have tried their methods and have

* From the Russell Sage Institute of Pathology in affiliation with the Second Medical Division of Bellevue Hospital.

1. Barr, D. P., and Du Bois, E. F.: Clinical Calorimetry, Paper 28, The Metabolism in Malarial Fever, Arch. Int. Med. **21**:627 (May) 1918.

2. Kraus, Fr., and Chvostek, F.: Ueber den respiratorischen Gaswechsel im Fieberanfall nach Injection der Koch'schen Flüssigkeit, Wien. klin. Wchnschr. **4**:104, 1891.

3. Freund, H., & Schlagentweit, E.: Ueber die Waerme Regulation Kurarierter Tiere, Arch. f. Exper. Path. u. Pharmacol. **69**:12, 1912.

4. Verzar, Fritz.: Die Wirkung intravenöser Kochsalzinfusionen auf den respiratorischen Gaswechsel, Biochem. Ztschr. **34**:41, 1911.

5. Berrar, M.: Die Wirkung des Aloins auf den Stoffwechsel, Biochem. Ztschr. **49**:426, 1913.

6. Miller, J. L., and Lusk, F. B.: The Treatment of Arthritis by Intravenous Injection of Foreign Protein, J. A. M. A. **66**:1756 (June 3) 1916; The Use of Foreign Protein in the Treatment of Arthritis, J. A. M. A. **67**:2010 (Dec. 30) 1916.

investigated the physiologic changes which accompany the paroxysm. Cecil⁷ has made a clinical study of forty cases treated in this hospital, including in his series the cases published in this article. He obtained fairly satisfactory results but did not consider that treatment with foreign proteins was indicated until salicylates had been given a thorough trial. Snyder⁸ used the same New York City Board of Health typhoid vaccine, starting with small doses.

Scully⁹ made a careful study of the blood count, temperature and blood pressure after intravenous injections and published composite curves which are most instructive. He used typhoid vaccine in doses of from 37 to 75 million bacilli with patients suffering from acute articular rheumatism. The composite temperature curve reached a maximum of 103.6 F. four hours after the injection and fell gradually to normal in sixteen hours. The highest individual temperature was 106.6 F.; the lowest 102 F. The leukocytes showed first a fall and then a sharp rise. The average count was 14,000 at the time of injection. During the chill it dropped to 5,000 but rose to 40,000 about eight hours after the vaccine was given. The highest individual count was 77,200 at six hours; the lowest 13,600. The blood pressure probably rose during the chill but accurate measurements were impossible. After the chill, the composite curve showed a fall, reaching 92 mm. systolic and 60 mm. diastolic pressure six hours after the injection. Following this there was a gradual rise. The lowest individual reading was 60 mm. systolic and 40 mm. diastolic, the patient evidently suffering from marked shock. In addition to these phenomena, Scully examined the urine but found no marked changes.

Cowie and Calhoun¹⁰ have emphasized the analogy between the nonspecific chill and the malarial paroxysm. They made numerous blood counts and found nucleated red cells and myelocytes and many atypical cell forms, particularly in the lymphocyte group. Jobling, Petersen and their co-workers¹¹ have studied in detail the ferments after the injection of foreign protein. They have found an instantaneous mobilization of a large amount of nonspecific protease; decrease in antiferment; increase in noncoagulable nitrogen of the serum; increase in amino-acids; and a primary decrease in serum

7. Cecil, R. L.: A Report on Forty Cases of Acute Arthritis Treated by Intravenous Injections of Foreign Protein, *Arch. Int. Med.* **20**:951 (Dec.) 1917.

8. Snyder, R. G.: A Clinical Report of Nonspecific Protein Therapy in the Treatment of Arthritis, *Arch. Int. Med.* **22**:224 (Aug.) 1918.

9. Scully, F. J.: The Reaction after Intravenous Injections of Foreign Proteins, *J. A. M. A.* **69**:20 (July 7) 1917.

10. Cowie, D. M., and Calhoun, H.: Nonspecific Therapy in Arthritis and Infections, *Arch. Int. Med.* **29**:69 (Jan.) 1919.

11. Jobling, J. W.: Petersen, W., and Eggstein, A. A.: Studies on Ferment Action, *J. Exper. M.* **22**:401, 568, etc., 1915; Petersen, Wm. H.: Serum Changes Following Protein "Shock" Therapy, *Arch. Int. Med.* **20**:716 (Nov.) 1917.

proteoses. There is also an increased flow of lymph from the thoracic duct. Later there is a progressive increase in the noncoagulable nitrogen, in proteoses and serum lipase.

We must remember that while all these changes are taking place in the blood and cardiovascular system, the organism is being subjected to great variations in the degree of muscular activity, marked fluctuations in the respiratory activity, sudden demands for the mobilization of foodstuffs with increased products of katabolism, and also rapid changes in the temperature of the body cells. These metabolic and physical phenomena form the subject of the present investigation.

The apparatus used was the respiration calorimeter described in the previous papers of this series and the patients were kept under close observation in the metabolism ward. On account of the length of the observations, it was necessary to allow them some food shortly before the start of the experiment. All, with the exception of Albert G., were given a small "standard breakfast" four or five hours before the start of the observation. It has been shown in Paper 26¹² of this series that this breakfast has no effect on the metabolism, except for two or three hours after it has been taken.

The subjects were five patients with various rheumatic affections, one comparatively well man with lumbar and sciatic pains and one normal control. Three of the patients were studied from the standpoint of possible changes in metabolism which might occur in chronic arthritis. The results of observations on their basal metabolism may be found in the accompanying article on arthritis. At the time of the observations there were in the general wards of the hospital a considerable number of patients being treated with intravenous injections of protein made according to the method of Jobling or with typhoid vaccine as prepared by the New York City Board of Health. The other two rheumatic subjects were intelligent men selected from among these patients. Both had previously given definite response to injections of foreign protein. In these, it seemed possible to calculate fairly closely the time interval between a given dose and the onset of a chill. This was a matter of importance since the technic of managing a calorimeter in short periods during a chill is extremely difficult. With one subject (Genaro A.), a rise in temperature followed the injection but the chill did not occur. Albert G., the normal control, and R. L. C., had never been given foreign protein before; yet, neither had the expected chill. All of the others reacted very much in the manner predicted.

12. Soderstrom, G. F.; Barr, D. P., and Du Bois, E. F.: Clinical Calorimetry, Paper 26, The Effect of a Small Breakfast on Heat Production, *Arch. Int. Med.* **21**:613 (May) 1918.

Fig. 1 — Temperature curve of William B.

TABLE 1.—

Subject, Date, Weight, Surface Area, Linear Formula	Period	End of Period, Time	Carbon Dioxid, Gm.	Oxygen, Gm.	R. Q.	Water, Gm.	Urine N per Hour, Gm.	Indirect Calo- rimetry, Cal.	Heat Elimi- nated, Cal.
R. L. C.*.....	Prelim.	11:48							
1/19/17, 62.3 Kg. (Ht.-Wt.) 1.77 Sq. M.	1	1:48	46.4	43.1	0.78	57.9	0.49	142.3	
William B.	Prelim.	11:40							
1/15/17 66.2 Kg. 1:80 Sq. M.	1	12:20	24.1	20.2	0.87	22.3	0.43	68.6	50.1
	2	12:50	39.0	32.6	0.87	26.4	0.43	111.2	49.4
	3	1:50	24.3	28.4	0.62	40.0	0.43	92.8†	88.9
	4	2:50	28.6	26.8	0.78	39.5	0.43	88.8	92.5
Albert G.	Prelim.	1:07							
1/13/15 66.8 Kg. 2.07 Sq. M. Meeh Formula	1	2:07	22.5	19.0	0.86	28.0	0.48	64.0	69.0
	2	3:07	26.7	21.2	0.92	29.7	0.42	72.5	74.1
	3	4:07	25.2	23.8	0.77	30.2	0.42	78.6	78.8
	4	5:07	25.0	22.7	0.80	31.2	0.42	75.4	73.2
John Br.	Prelim.	11:29							
2/2/17 58.5 Kg. 1.75 Sq. M. (Ht.-Wt.)	1	12:19	54.8	44.7	0.89	29.0	0.68	132.8	70.6
	2	12:49	16.8	14.3	0.86	15.9	0.68	48.5	43.2
	3	1:19	15.6	13.8	0.82	15.6	0.68	46.4	44.1
	4	2:19	31.7	31.0	0.74	32.1	0.68	102.1	93.5
	5	3:19	31.4	28.8	0.79	46.9	0.68	96.1	112.2
Joseph McC.	Prelim.	11:09							
2/7/17 51.4 Kg. 1.46 Sq. M.	1	12:09	20.9	18.6	0.82	27.8	0.27	62.4	61.5
	2	12:46					0.27		
	3	1:15	8.8	10.1	0.79	13.4	0.27	58.2	27.8
	4	1:41	10.4	7.4		13.8	0.27		28.6
	5	2:41	29.6	27.0	0.80	32.6	0.27	90.3	66.1
	6	3:41	22.7	21.9	0.76	30.6	0.27	72.1	66.4
	Aver.								
Joseph McC.	Prelim.	9:28							
2/12-13/17 51.6 Kg. 1.46 Sq. M.	1	9:58	10.7	8.9	0.87	9.8	0.16	30.3	26.3
	2	10:20	7.8	6.2	0.91	7.7	0.16	21.1	20.6
	3	11:00	28.1	22.4	0.92	17.6	0.16	77.1	44.6
	4	12:00	23.3	20.7	0.82	24.5	0.16	69.7	62.8
	5	1:00	27.1	23.4	0.84	27.2	0.16	79.3	68.7
	6	1:40							
	7	2:40	22.4	19.7	0.83	26.3	0.16	66.5	69.3
	8	3:40	21.3	19.0	0.82	29.8	0.16	63.7	75.3
	9	4:40	20.7	18.2	0.83	26.7	0.16	61.3	68.8
	10	5:30	18.8	17.0	0.81	23.9	0.16	56.7	63.6
	11	6:00	10.7	9.1	0.85	12.9	0.16	30.8	34.0

* Direct lost because of leak in pipes of ice tank.

† Spirometer string broke in first and third periods.

‡ Calculated from R. Q. of 0.70.

—CALORIMETER DATA

Direct Calorimetry (Rectal Temp.), Cal.	Rectal Temp., Cal.	Average Pulse	Work Added, Cm.	Non-protein R. Q.	Per Cent. Calories from			Calories per Hour		Remarks
					Protein	Fat	Carbohyd.	Per Kg.	Per Sq. M. (Linear)	
....	36.6	..	..		..	..	..			Proteose 4% (Jobling) 0.5 c.c. at 10:05 a. m.
....	36.9	..	32	0.78	18	62	20	1.13	40.2	Quiet, no chill
....	37.3	..	..		..	..	..			Proteose 4% (Jobling) 0.8 c.c. at 9:18 a. m.
67.4	37.6	60	34	0.88	11	87	52	1.55	57.2	Shivering last 5 min.
104.0	38.6	..	21	0.87	20	26	54	3.36	123.5	Chill 12:20-12:40
115.4	39.1	79	14	0.60	..	..	..	1.40		Fairly quiet
62.6	38.6	76	14	0.77	13	48	39	1.34	49.3	Quiet
....	36.8	..	..		..	..	..			Typhoid vaccine 500 million subcutaneous-ly 10:07 a. m.
64.2	36.7	65	13	0.90	20	27	53	0.96	30.9	Quiet
90.5	37.0	60	28	0.94	15	17	68	1.09	35.0	Quiet
77.3	37.0	60	24	0.76	14	70	16	1.19	37.9	Rather restless
74.4	37.0	..	28	0.80	15	58	27	1.13	36.4	Rather restless
....	37.8	..	..		..	..	..			Typhoid vaccine 25 million intravenously at 10:50 a. m.
139.6	39.2	..	25	0.90	10	30	60	3.14	105.0	Chill, 30 min.
76.1	39.9	..	10	0.87	19	35	46	1.64	54.8	Quiet, voided
38.2	39.8	..	7	0.82	20	48	22	1.58	52.6	Quiet
87.6	39.7	..	20	0.73	18	76	6	1.73	57.7	Quiet
86.0	39.2	98	33	0.79	19	60	21	1.63	54.5	Somewhat restless
....	37.5	..	..		..	..	..			Basal
60.3	37.5	64	23	0.82	..	..	..	1.21	42.7	Very quiet
....	37.5	..	..		..	..	..			Removed from calorimeter, typhoid vaccine 40 million intravenously at 12:31 p. m.
20.4	37.3	58	12	0.79	..	..	..	1.24	40.7	Quiet
29.4	37.3	56	8	0.79	..	..	..	1.24	40.7	Quiet
112.0	38.4	..	12	0.79	..	..	..	1.76	57.9	Chill, 1:45-2:15 p. m.
79.0	38.8	..	..	0.75	..	..	..	1.40	46.2	Very quiet
....		..	..		10	65	25			
....	37.2	..	..		..	..	..			Typhoid vaccine 50 million intravenously at 9:05 p. m.
18.0	37.1	72	8	0.88	7	37	56	1.18	41.5	Quiet
20.5	37.1	..	2	0.90	8	30	62	1.11	39.5	Very quiet
92.8	38.2	89	7	0.92	4	26	70	2.24	79.3	Chill, 10:21-10:53 p. m.
70.2	38.4	120	..	0.82	6	58	36	1.35	47.7	Quiet
78.3	38.3	..	20	0.84	5	52	43	1.53	54.3	Fairly quiet
....	38.5	..	..		..	..	..			Removed from calorimeter, given 240 c.c. water at 1:05 (37°)
57.4	38.2	79	9	0.83	6	56	38	1.29	45.5	Very quiet
62.2	37.9	..	7	0.82	7	57	36	1.23	43.6	Asleep
62.0	37.8	88	4	0.83	7	53	40	1.19	42.0	Very quiet
59.9	37.7	..	13	0.81	6	62	32	1.32	46.4	Very quiet
30.9	37.6	..	8	0.86	7	51	42	1.20	42.2	Restless last 5 min.

TABLE 1.—CALORIMETER—

Subject, Date, Weight, Surface Area, Linear Formula	Period	End of Period, Time	Carbon Dioxid, Gm.	Oxygen, Gm.	R. Q.	Water, Gm.	Urine N per Hour, Gm.	Indirect Calo- rimetry, Cal.	Heat Elimi- nated, Cal.
Frank G.†..... 2/23/17 56.7 Kg. 1.56 Sq. M.	Prelim.	11:15							
	1	11:45	11.0	9.9†	0.81	20.7	0.29	33.2	32.8
	2	12:45	40.9	35.6	0.84	37.7	0.29	120.1	68.6
	3	1:45	26.0	23.1†	0.82	38.5	0.29	77.4	74.0
	4	2:45	25.2	24.4	0.75	51.0	0.29	80.3	90.6
	5	3:53	24.1	27.5	0.64	73.8	0.29	89.7	110.1
Genaro A..... 3/2/17 52.9 Kg. 1.56 Sq. M.	Prelim.	11:15							
	1	11:45	12.1	9.9	0.89	12.9	0.68	33.3	32.1
	2	12:15	13.2	11.9	0.80	15.6	0.68	39.4	37.7
	3	1:15	25.9	23.5	0.80	32.3	0.68	77.7	68.7
	4	2:15	26.2	25.0	0.76	33.8	0.68	82.0	71.1
	5	3:15	27.2	26.2	0.76	36.5	0.68	85.8	78.7

* Direct lost because of leak in pipes of ice tank.

† Spirometer string broke in first and third periods.

‡ Calculated from R. Q. of 0.70.

CASE HISTORIES

CASE 1.—R. L. C., a physician, born in the United States, 35 years of age, has never been seriously ill, has had no attacks of tonsillitis or of articular rheumatism. During the winter of the past three or four years he has had lumbar and sciatic pains, which, at times, have entirely incapacitated him. At the time of the observation he was in the midst of a particularly uncomfortable attack.

Physical Examination.—Nothing abnormal. Tonsils are small and healthy in appearance. The teeth are in good condition. No areas of tenderness are found in the back or in the region of the sciatic nerve.

Jan. 19, 1917, he was given intravenously 0.5 c.c. of a 4 per cent. solution of Jobling's proteose. No rise in temperature or disagreeable symptoms followed the injection. No improvement of pain or stiffness resulted.

The calorimeter observation was unsatisfactory because there was no chill. A leak in the pipe made it impossible to use the method of direct calorimetry in this experiment.

CASE 2.—William B., arthritis deformans (gonorrheal?), a traveling salesman, born in the United States, 50 years of age, was admitted Oct. 16, 1916, and discharged improved Jan. 17, 1917. In 1899 he had gonorrhea followed by epididymitis. The discharge lasted for two weeks. He had had occasional sore throat but no previous attacks of joint pain.

July 21, 1916, he was seized with pain in the left arm and wrist and in the right ankle. Two days later he went to St. Vincent's Hospital where he was treated until Oct. 16.

Physical Examination.—He is a poorly nourished, well developed rather apathetic man. He has no temperature and is not toxic. The right elbow is ankylosed and is very painful. All of the muscles of the right arm and forearm are flabby and wasted. The fingers of the right hand are stiff from disuse. The right shoulder, left elbow and right ankle are very moderately involved. There is superficial edema of the feet and ankles.

—DATA— (Continued)

Direct Calorimetry (Rectal Temp.), Cal.	Rectal Temp., Cal.	Average Pulse	Work Adder, Cm.	Non-protein R. Q.	Per Cent. Calories from			Calories per Hour		Remarks
					Protein	Fat	Carbohyd.	Per Kg.	Per Sq. M. (Linear)	
....	37.5	..	..		..	..	..			Typhoid vaccine 35 million intravenously at 10:51 a. m.
29.8	37.4	84	7	0.81	10	58	32	1.18	42.6	Quiet, asleep
150.7	39.1	96	..	0.84	6	51	43	2.12	77.0	Chill, 11:58 a. m. - 12:25 p. m.; drank 240 c.c. water (37°C.) 12:37 p.m.
76.5	39.2	96	19	0.82	10	54	36	1.37	49.6	Restless for 50 min.
75.2	38.9	..	6	0.75	10	77	13	1.42	51.5	Restless last 10 min.
93.0	38.6	..	18	0.62	..	..	..	1.58	57.5	
....	37.6	..	..		..	..	..			Typhoid vaccine 20 million intravenously at 10:50 a. m.
32.0	37.6	66	1	0.92	27	20	53	1.26	42.7	Very quiet
40.4	37.7	..	5	0.80	23	44	33	1.50	50.5	Almost motionless
85.0	38.1	..	3	0.80	23	52	25	1.47	49.8	Almost motionless
80.5	38.3	74	3	0.75	22	68	10	1.55	52.6	Almost motionless
76.5	38.3	..	2	0.74	21	70	9	1.62	55.0	Almost motionless

November 27 he had an acute attack of follicular tonsillitis from which he recovered rapidly. From December 19 to January 15 he received at rather irregular intervals eight doses of Jobling's proteose intravenously. From the first dose he had no reaction. Both the first and second injections were of a 1 per cent. solution; the others were of a 4 per cent. solution, varying in dose from 0.3 c.c. to 1.0 c.c.

January 10 and January 15 he was observed in the calorimeter following proteose injections. Owing to technical errors, the observation of January 10 was lost. That taken on the fifteenth is here presented. No marked change in symptoms was noted after any of the proteose injections. The joint condition improved very gradually. With constant baking and massage he regained motion in the fingers of the right hand. The elbow was still ankylosed at the time of discharge, January 17.

CASE 3.—Albert G., a normal control to whom typhoid vaccine was given subcutaneously, a laborer born in Italy, 24 years of age, was admitted Dec. 14, 1914, and discharged Jan. 14, 1915. His health was excellent. He was out of work and was admitted to the hospital to act as a normal control for other observations which were being carried on at the time. He was short, with large muscles and very little subcutaneous fat. He was neurasthenic, continually fearing that he would become ill.

January 13, at 10:07 a. m., he was given 500 million dead typhoid bacilli (New York City Board of Health vaccine) subcutaneously into the arm. The usual reaction occurred with moderate swelling and tenderness of the arm.¹³

CASE 4.—John Br., acute arthritis, gonorrheal (rheumatic?), a clerk born in the United States, 19 years of age, was admitted Jan. 25, 1917, and discharged

13. For details of previous observations on this man, consult Soderstrom, G. F.; Meyer, A. L., and Du Bois, E. F.: Clinical Calorimetry, Paper 11, A Comparison of the Metabolism of Men Flat in Bed and Sitting in a Steamer Chair, Arch. Int. Med. **17**:872 (July) 1916; Gephart, F. C., and Du Bois, E. F.: Clinical Calorimetry, Paper 13, The Basal Metabolism of Normal Adults with Special Reference to Surface Area, Arch. Int. Med. **17**:902 (June) 1916.

improved March 23, 1917. January 7 he began to have a urethral discharge. Six days later he was seized with pain in the right knee, right foot, left foot and right thumb.

Physical Examination.—Patient was a well developed, somewhat emaciated boy, acutely ill, rather toxic. The tongue was slightly dry, with a brown coat. The left knee joint is distended with fluid, hot, slightly tender and held in semiflexion. The right knee, both ankles and some of the small joints of the hands and feet show swelling and moderate tenderness. There is a urethral discharge containing gonococci in large numbers.

January 29 and January 31 he was observed in the calorimeter, February 2 he was given intravenously a 25 million dose of New York City Board of Health typhoid vaccine and was observed in the calorimeter. On the fourth and again on the fourteenth he received typhoid vaccine. On March 1 he was discharged to the general ward, very slightly improved by the vaccine therapy. He was later given gonococcus vaccine intravenously. Following this his improvement was rapid. He was discharged from the hospital March 23 with slight swelling in his right knee joint but with no other symptoms.

CASE 5.—Joseph McC., subacute gonorrheal arthritis, an elevator operator, born in the United States, 27 years of age, was admitted Jan. 24, 1917, and discharged unimproved. In 1910 he had an attack of gonorrheal urethritis followed by epididymitis. Since then he has had a urethral discharge several times, the last time being in November, 1916. In 1912 he had an acute arthritis involving all the joints and he was ill for nine weeks. A second attack of the same character, in 1914, lasted two months. He has never had sore throat, chorea or other manifestations of acute rheumatic fever.

Jan. 3, 1917, he began to have a dull pain in the lower end of the spine and in the lumbosacral muscles which radiated down the right thigh. His right heel became so painful that he could not walk. About the same time the urethral discharge recommenced.

Physical Examination.—This shows an under developed, poorly nourished man. He holds himself very stiffly because of pain in the back. There is pain on pressure over the sacrococcygeal joint and marked tenderness over the spine of the ninth dorsal vertebra. The under surface of the right heel is exquisitely tender. There is considerable watery purulent urethral discharge, a smear of which shows gonococci. The prostate is moderately enlarged. The right seminal vesicle is palpable.

Urine from both anterior and posterior urethra contains pus but no albumin or casts. Gonococcus fixation test is negative. Wassermann reaction is negative. Roentgen ray shows periosteal exostosis of the os calcis of both heels.

His symptoms remained unchanged during the first seven days in the hospital. February 1 he was given intravenously 40 million of the New York City Board of Health typhoid vaccine. On the third, the fifth and the seventh similar doses were given. The character of the reactions following the injections appears on the temperature chart. The chills began from thirty to seventy-five minutes after the injection. On the thirteenth a dose of 50 million was given. On the seventh and thirteenth the patient was observed in the calorimeter. No noticeable improvement resulted from the vaccine therapy. On the first day following each injection he was more stiff and uncomfortable. On the second day the condition returned to that which obtained before the vaccine was given. He was discharged improved.

CASE 6.—Frank G., chronic gonococcus arthritis, a barber, born in the United States, 42 years of age, a widower, was admitted Feb. 13, 1917, to the service of Dr. C. E. Nammack, transferred to the Metabolism Ward and discharged unimproved May 8, 1917. He says he has had gonorrhea seven times, the first attack being at the age of 15. He has had three distinct attacks of arthritis, all of which had occurred during or immediately following an acute arthritis.

During the past year the joint pains have been almost constant. Since January, 1917, he has had a urethral discharge and more severe joint involvement. He has always used alcohol to excess. (During the past month he has consumed as much as a quart of whisky a day). February 16, in another ward, he received intravenously a 20 million dose of New York City Board of Health typhoid vaccine. February 19 he received 30 million. The joint condition was not improved but the urethral discharge, which had been profuse, was checked. He is a poorly nourished, fairly well developed, very dissipated looking man. He has no temperature elevation and does not appear to be toxic. His throat is congested. The tonsils are normal in appearance and his teeth are in fair condition. His spleen is felt two finger breadths below the costal margin. He has moderate pain, tenderness and swelling in the right wrist, right hand and right knee. His prostate is enlarged. Massage of this organ causes the discharge of a drop or two of thin, purulent material which contains large numbers of gonococci.

His gonococcus fixation test is strongly positive. Wassermann is negative.

February 27 he was transferred to the general service. March 10 the urethral discharge again became profuse. March 27 he developed a severe gonorrheal conjunctivitis. He had entirely recovered from this at the time of his discharge May 8. The joint condition, however, was unimproved.

CASE 7.—Genaro, A., acute rheumatic fever, a munition factory worker, born in Cuba, 22 years of age, was admitted to the hospital Feb. 25, 1917, and discharged improved March 16, 1917. He says that he has never been ill before. He denies gonorrhea and syphilis.

Since February he has had pain in both knees, wrists, shoulders, elbows and ankles. With it, he has had a slight sore throat, some headache, and at the onset of the illness several nose bleeds. March 26 he received intravenously in another ward a 60 million dose of New York City Board of Health typhoid vaccine; March 27, 50 million; and March 28, 50 million. He had severe reactions in each case. After the first injection there was considerable clinical improvement. The other doses had little or no effect.

Physical Examination.—He is a well nourished and developed Cuban boy of remarkably sanguine disposition in spite of considerable pain. He is not toxic. The tongue is moist. His tonsils are small and not inflamed. The teeth show many fillings and gold crowns. At the time of admission his heart was normal but later there developed a soft, blowing, systolic murmur, maximum at the apex and transmitted outward into the axilla. The spleen is felt one fingerbreadth below the costal margin. The left wrist, elbow and shoulder are painful on motion.

March 2, after receiving a 20 million dose of typhoid vaccine, he was observed in the calorimeter. He had no chill. On the third, fourth and sixth he received a dose of 40 millions. Each time he had a chill with severe reaction. The joint pains gradually improved. Improvement, however, seemed to bear no definite relation to treatment. After the last injection his temperature reached normal and remained so until his discharge March 16. At that time all joint pain and swelling had disappeared but the heart murmur persisted.

In all, eight observations were made, lasting from two to eight and a half hours. When changes in the metabolism were expected the periods were made as short as possible. One period of only twenty-two minutes was obtained. It would have been interesting to subdivide the period of chill but no experimental period can be ended unless the subject has been quiet for six or seven minutes. Short periods are not as accurate as long ones since a small error in determining the

Fig. 2.—Temperature curve of Genaro A.

residual carbon dioxide or oxygen will cause a larger percentage change in the shorter period. This error will, of course, be compensated for in the next period.

The time of the chill never corresponds exactly to the experimental period in which it is observed. It is possible, however, to calculate with fair accuracy the heat production occurring during the chill itself. We may consider that the metabolism during the few minutes before the chill is at the same level as that of the preceding period. Similarly the metabolism in the short interval after the paroxysm approximates the level of the following period. The heat thus calculated for the interval before and after the chill is subtracted from the total heat produced during the entire experimental period. In this manner, the heat production during a twenty minute chill can be estimated even though the experimental period be forty minutes long.

The data of the calorimetric experiments are given in Table 1. Figure 3 shows graphically the results of the calorimeter observation on John B. Figures 4 and 5 show the results on Joseph McC. (Case 5). Figure 6 on Frank G. (Case 6); Figure 7 on William B. (Case 2); Figure 8 on Genaro A. (Case 7).

DISCUSSION OF RESULTS

The phenomena observed after the intravenous injection of foreign protein are almost identical with those observed in malaria.¹ For convenience of discussion the malarial paroxysm was divided into six periods: (a) a basal period before the chill; (b) a prodromal phase immediately before the chill; (c) the chill itself; (d) a period of rising temperature after the cessation of shivering; (e) a period of high continuous temperature corresponding to the clinical stage of heat, and, finally, (f) a period of falling temperature. In considering the reactions to foreign proteins, this same division is useful.

In the chills of malaria, the respiratory quotients were found to be high. The same thing is observed during the chill following the injection of vaccines, which indicates a rapid combustion of the glycogen stores of the body. In most of the experiments, the quotient falls steadily after the chill.

Four main questions of the mechanism of the rise and fall of body temperature will be considered.

1. The relation of heat production to heat elimination as factors in the rise and fall of temperature.

2. The divergence of the rectal temperature from the average body temperature.

3. The relation of heat lost in the vaporization of water to the total heat elimination and to the heat production.

4. The influence of body temperature on heat production.

The data on which the discussion is based are presented in Table 2.

TABLE 2.—SUMMARY OF DATA ON HEAT REGULATION

Name; Date; Surface Area	Condition of Patient	Length of Period	Rectal Tempera- ture, C.	R. Q.	Heat		Per Cent. Diver- gence of Direct from Indirect, Cal.	Change in Rectal Temper- ature	Change in Average Body Temper- ature	Per Cent. Total Heat Lost in Vap. of Water	Per Cent. Heat Pro- duced Lost in Vap. of Water	Calories per Square Meter per Hour	Per Cent. Rise Above Normal Basal for Age
					Pro- duced Ind.	Elimi- nated							
John B. . . 7/2/17. 1.75 Sq. M.	Chill.	50 minutes	37.8-39.2	0.89	152.5	70.6	-8.5	+1.4	+1.69	24.1	11.1	105.0	+156
	Rising temperature after chill.	30 minutes	39.2-39.9	0.86	48.1	43.2	+58.0	+0.7	+0.10	21.6	19.4	54.8	+34
	High continuous temperature.	90 minutes	39.9-39.7	0.78	137.6	137.6	-11.7	-0.2	+0.20	20.4	19.2	55.2	+35
Joseph Mc. 7/7/17. 1.46 Sq. M.	Falling temperature.	60 minutes	39.7-39.2	0.79	95.4	112.2	-9.8	-0.5	-0.35	24.5	23.8	54.5	+33
	Afebrile before vaccine.	60 minutes	37.5-37.5	0.82	62.4	61.5	-3.4	±0.0	+0.02	26.5	26.1	42.7	+8
	Afebrile after vaccine but be- fore chill.	55 minutes	37.5-37.3	0.79	58.2	56.4	-14.4	-0.2	+0.04	23.3	27.4	40.7	+30
Joseph Mc. 2/12/17. 1.46 Sq. M.	Chill.	60 minutes	37.3-38.4	0.80	90.3	66.1	+24.0	+1.1	+0.57	23.9	24.9	57.9	+49
	Rising temperature after chill.	60 minutes	38.4-38.8	0.76	72.1	66.4	+9.0	+0.4	+0.13	27.0	19.0	46.2	+17
	Afebrile before chill.	52 minutes	37.2-37.1	0.89	51.4	46.9	-5.7	-0.1	+0.10	21.9	20.1	40.5	+3
Genaro A. . . 3/2/17. 1.56 Sq. M.	Chill.	40 minutes	37.1-38.2	0.92	77.1	44.6	+26.0	+1.1	+0.78	23.2	13.4	79.3	+101
	Rising temperature after chill.	2 hours	38.2-38.6	0.83	149.0	131.5	-0.4	+0.4	+0.40	23.3	20.5	51.0	+29
	Falling temperature.	4 hrs. 20 m.	38.5-37.6	0.83	274.0	304.0	-2.4	-0.9	-0.58	23.4	25.1	43.9	+11
William B. 1/15/17. 1.80 Sq. M.	Afebrile.	30 minutes	37.6-37.6	0.89	33.3	32.1	-3.9	±0.0	+0.03	23.5	22.7	42.7	+8
	Rising temperature without chill.	2 hrs. 30 m.	37.6-38.3	0.79	199.1	177.5	+3.0	+0.7	+0.49	26.5	23.9	51.5	+31
	High continuous temperature.	60 minutes	38.3-38.3	0.76	85.8	78.7	-10.8	±0.0	+0.17	27.2	24.9	55.0	+39
Frank G. . . 2/23/17	Rising temperature before chill	40 minutes	37.3-37.6	0.87	68.6	50.1	-1.7	+0.3	+0.34	26.1	19.1	57.2	+53
	Chill.	30 minutes	37.6-38.6	0.87	111.2	49.4	-6.5	+1.0	+1.13	32.1	14.2	123.5	+229
	Falling temperature.	60 minutes	39.1-38.6	0.78	88.8	92.5	-29.5	-0.5	-0.07	24.8	26.0	49.3	+31
Frank G. . . 2/23/17	Afebrile before chill.	30 minutes	37.5-37.4	0.81	33.2	32.8	-10.2	-0.1	+0.01	37.0	36.5	42.6	+11
	Chill.	60 minutes	37.4-39.1	0.84	120.1	68.6	+26.0	+1.7	+1.09	32.2	18.4	77.0	+100
	High continuous temperature.	60 minutes	39.1-39.2	0.82	77.4	74.0	-1.2	+0.1	+0.07	30.5	39.2	49.6	+29
	Falling temperature.	60 minutes	39.2-38.9	0.75	80.3	90.6	-6.3	-0.3	-0.22	33.0	37.2	51.5	+34

Relation of Heat Production to Heat Elimination.—In malaria, it was found that during a chill the heat production was enormously increased while the heat elimination remained practically at its basal level. After injection of foreign protein, the same mechanism is observed. It would seem as if the temperature regulation were set at a higher level and that the body responded by producing heat sufficient to warm the tissues to the new temperature level. After

Fig. 3.—Calorimeter observation on John Br., February 2. At 10:50 a. m., 25 million typhoid bacilli were given intravenously. The chill lasted from 11:40 a. m. to 12:10 p. m. The upper curve shows the rectal temperature measured every four minutes; the dash line below shows the change in the average body temperature, as calculated from the difference between heat elimination and heat production as determined by the method of indirect calorimetry. This line is started arbitrarily 0.5 C. lower than the rectal temperature. While it is possible to determine the rise and fall of the average body temperature, it is absolutely impossible to fix the exact level at which these fluctuations take place. After the start at 11:29 a. m., the first satisfactory fixation of this line was at 12:49 p. m. Between these points the exact shape of the curve is not certain. The respiratory quotient (R. Q.) is indicated by short lines in each period. The line at 80.8 calories represents the basal heat production per hour as determined on January 31.

vaccine, the heat production is increased from 75 to 210 per cent. during the chill, while the amount of heat eliminated is scarcely increased above its former basal level. This, of course, results in the storage of large amounts of heat within the body. After the chill is over, the heat production drops sharply but still remains somewhat above the normal, as is usually the case during increased body temperature. The rectal temperature still continues to rise after the shivering ceases. The heat elimination is practically unchanged. During the

Fig. 4.—Calorimeter observations on Joseph McC., February 7. The first period from 11:09 a. m., to 12:09 p. m., was a basal determination. At 12:31 p. m. he was given an intravenous injection of 40 million typhoid bacilli. Two short periods were obtained before the chill, which lasted from 1:45 to 2:15 p. m. Note that the average body temperature rises more slowly than the rectal temperature.

stage of high continuous temperature the heat elimination increases until it is equal to the heat production; both, however, being at a level from 20 to 40 per cent. above the normal. During the fall in body temperature, the heat production drops gradually to the basal level and the heat elimination increases steadily.

Relation of Rectal to Average Body Temperature.—During the past ten years, more than 300 observations on patients with normal

Fig. 5.—Calorimeter observation on Joseph McC., February 12 and 13. At 9:05 p. m. he was given 50 m from 10:21 to 10:53 p. m. At 1:00 a. m. the calorimeter was opened to give the patient a drink of water. It 1:40 a. m. Note that the curve for the average body temperature lags behind that of the rectal temperature

February 12 and 13. At 9:05 p. m. he was given 50 million typhoid bacilli intravenously. The chill lasted
 ter was opened to give the patient a drink of water. It was closed immediately and the next period started at
 temperature lags behind that of the rectal temperature.

temperature have been made with the Sage calorimeter. They have shown a remarkably close agreement between the direct and indirect methods of measuring heat production. In patients with fever, however, and particularly in malaria, there has been a wide divergence between the two methods. This may be explained on the following basis. The measurement of heat production by direct calorimetry depends for one of its factors on the rectal temperature which in the

Fig. 6.—Calorimeter observation on Frank G., February 23. At 10:51 a. m. 35 million typhoid bacilli were given intravenously. The chill lasted from 11:58 a. m. to 12:25 p. m. The average body temperature rose less sharply than the rectal temperature.

calculation is assumed to represent accurately the average temperature of the body. During rapid production of heat, such as is seen during a shivering chill, the distribution of heat will not be immediately uniform, with the result that the temperature in the rectum may change more or less than that of the rest of the body.

Exact measurement of average body temperature appears impossible since we cannot have thermometers in all parts of the body. In the paper on malaria, however, an indirect method was devised which allows us to calculate this value. For a given interval the difference

Fig 7.—Calorimeter observation on William B., January 15. At 9:40 a. m. he was given an intravenous injection of 0.8 c.c. of a 4 per cent. proteose solution. He shivered during the last five minutes of the first period and had a violent chill from 12:20 to 12:40 p. m. In this case the average body temperature seems to have risen more sharply than the rectal temperature.

is taken between the number of calories produced, as estimated by the chemical methods of indirect calorimetry and the calories eliminated as measured by the direct physical methods. This represents the heat lost or gained by the whole body. When this difference is divided

by the hydrothermal equivalent of the organism, the gain or loss in average body temperature is obtained. For example, heat production 100 calories, minus heat elimination 60 calories=heat stored 40 calories. In a man weighing 70 kg., the hydrothermal equivalent (heat necessary to raise the temperature of the whole body 1 C.)= 58.1 calories.¹⁴ The gain in average body temperature is, therefore, $\frac{40}{58.1} = 0.66$ C. This may be compared with the change in rectal temperature which has been observed during the corresponding time interval.

In Figures 3 to 8, the average body temperature, as calculated by this method, is plotted with the rectal temperature. In about half of the cases, the two methods agree during the chill. In the others,

Fig. 8.—Calorimeter observation on Genaro A., March 2. This patient received a small dose of 20 million typhoid bacilli intravenously at 10:50 a. m. He did not have a chill. There was only a slight rise in rectal temperature and even less of a rise in the average body temperature.

the finding is similar to that observed in malaria. The rectal temperature rises more rapidly than the average body temperature. During the period of falling temperature, the heat measurements in the rectum represent with fair accuracy the conditions of the entire body. In the previous discussion of malaria, it was considered that the more rapid rise of rectal temperature indicated a storing of heat in the deeper portions of the body during the chill. In the light of these further observations, however, this cannot be regarded as a con-

14. This value is obtained by multiplying the weight in kg. by the factor 0.83 which is assumed to represent the specific heat of the body.

stant finding. We can only say that, during rapid variations in the production and elimination of heat, the distribution is not always uniform and that the rectal temperature is often an inaccurate index of the average temperature of the body.

The Relation of Heat Lost in the Vaporization of Water to the Total Heat Elimination and to the Heat Production.—Under the constant temperature conditions of the calorimeter, normal individuals accomplish about 25 per cent. of their total heat elimination through the vaporization of water. The same relationship was found in a large number of observations made in afebrile pathologic conditions. With continuous normal temperature, heat elimination and heat production are equal so the calories lost in the vaporization of water also constitutes 25 per cent. of the heat production. During the sharp rise in temperature accompanying chill, we have seen that the heat production is greatly increased while the elimination remains at its normal level. It is conceivable that the heat lost in vaporization might follow either one. In malarial fever, it was found to bear a fairly constant relation to heat elimination. It never followed the curve of rapid fluctuation in heat production. In the present experiments, the same relation is observed (Table 2). During the chill, the calories lost in vaporization constitute a very low per cent. of the heat production. During the fall in temperature, the percentage may be high. The relation to heat elimination, on the other hand, never deviates far from the limits of normal. This is well illustrated in the experiment on John Br. where the heat lost in the vaporization of water varies between 11 and 28.8 per cent. of the heat production while the relation to heat elimination varies only between 20.4 and 24.5 per cent.

The ability of the body to utilize water in heat elimination is of the greatest importance in the regulation of temperature. Because of its high specific heat and fluid character, it is capable of absorbing large amounts of heat from the cells and of distributing it to the surface of the body where it may be eliminated. The dry skin and concentrated urine of acute fevers has often given rise to the belief that the mechanism of heat loss is disturbed.

During exercise, in exophthalmic goiter and in other conditions in which the heat production is increased, the heat elimination increases correspondingly. Wolpert,¹⁵ Benedict and Carpenter¹⁶ and others have shown that during exercise, the heat lost in vaporization is increased not only absolutely but relatively to the total heat elimination.

15. Wolpert: Ueber den Einfluss der Lufttemperatur auf die im Zustand anstrengender körperlicher Arbeit ausgeschiedenen Mengen Kohlensäure und Wasserdampf beim Menschen. Arch. f. Hyg. **26**:32, 1916.

16. Benedict, F. G., and Carpenter, T. M.: The Metabolism and Energy Transformations of Healthy Man During Rest. Carnegie Institute of Washington, Pub. 126, 1910.

Thus, in severe work involving a heat elimination four times the normal amount Benedict and Carpenter found that the calories lost in vaporization constituted 47.6 per cent. of the total. Such findings have been compared with those occurring during fever in which a relative increase in the vaporization calories does not always occur. This is one of the factors which has led Balcar, Sansum and Woodyatt¹⁷ to consider that fever may be due to an inability of the body to mobilize its water reserve for the elimination of heat. It has also been considered an argument for the supposed concentration of blood during fever.

It must be remembered that the rise in heat production involved in even light muscular work greatly exceeds the increase of heat production in fever. Except under conditions of chill, it is unusual to find the metabolism more than 50 or 60 per cent. above the normal

TABLE 3.—COMPARISON BETWEEN EXOPHTHALMIC GOITER AND TYPHOID FEVER IN THE PERCENTAGE OF TOTAL HEAT ELIMINATION LOST IN THE VAPORIZATION OF WATER

Subject	Diagnosis	Date	Heat Production, per Cent. Rise Above Average Normal Basal	Per Cent. Total Heat Elimination Lost in Vaporization of Water	Relative Humidity	
					Beginning	Ending
Morris S.	Typhoid.....	10/29/13	+41	24	49	49
Edwin T.	Goiter.....	3/10/15	+39	25	39	40
Charles F. ...	Typhoid.....	11/15/13	+37	23	37	47
Max W.	Goiter.....	4/24/14	+53	20	46	55
		3/23/14	+39	22	39	48
Edward B. ...	Typhoid.....	10/23/14	+28	23	41	38
Edwin T.	Goiter.....	3/ 6/15	+37	25	49	42

level during the course of a fever. It may be more in keeping, therefore, to compare water elimination in fever with some other conditions involving about the same increase in heat production. In Table 3 will be found a comparison of conditions in cases of exophthalmic goiter studied in Paper 14¹⁸ with those in cases of typhoid fever from Paper 7¹⁹ of this series. The temperature of the calorimeter was between 23 and 24 C. in all observations. Because the conditions or relative humidity were not always uniform the table is arranged in three groups of two each, showing respectively constant, rising and falling humidity.

17. Balcar, J. O.; Sansum, W. D. and Woodyatt, R. T.: Fever and Water Reserve of the Body, *Arch. Int. Med.* **24**:116 (July) 1919.

18. Du Bois, E. F.: Clinical Calorimetry, Paper 14, Metabolism in Exophthalmic Goiter, *Arch. Int. Med.* **17**:915 (June) 1916.

19. Coleman, W., and Du Bois, E. F.: Clinical Calorimetry, Paper 7. Calorimetric Observations on the Metabolism of Typhoid Patients with and Without Food, *Arch. Int. Med.* **15**:887 (June) 1915.

It is to be noted that all percentages in both conditions are close to the average normal value. Max W. with a metabolism higher than any of the fevered typhoid patients lost only 20 per cent. of his calories in the heat of vaporization. The comparison is more striking when one remembers the notoriously moist skin of goiter patients.

In the study of typhoid fever, it was found²⁰ that during a rising temperature, the percentage of heat lost in vaporization of water was slightly lower than normal. The average was 22 per cent. which must be compared with the average normal of 24 per cent. The variations in the typhoid group, however, were great and the number of cases small. In spite of this, the finding has been considered by others as evidence of the body's inability to mobilize water and hence as a cause of fever. That this is not a constant finding during the rising temperature of fever can be shown in the case of George S., a malaria patient, whose record is shown in Table 4.

TABLE 4.—RELATION OF HEAT VAPORIZATION TO TOTAL HEAT ELIMINATION IN GEORGE S., MALARIAL FEVER

Condition	Per Cent. Rise in Heat Production Above Average Normal Basal	Per Cent. Total Heat Elimination Lost in Vaporiza- tion of Water
Rising temperature before chill.....	+ 24	28
Chill.....	+216	31
Rising temperature after chill.....	+ 76	31
High continuous temperature after chill.....	+ 65	29
Falling temperature, profuse sweating.....	+ 40	36+

It will be seen that the percentage of heat lost in vaporization is well above the average normal not only during the rising temperature but also during the chill and following periods. The same thing is shown even more strikingly in the case of Frank G in Table 2. Similar results were obtained in all observations in erysipelas.

Our data present no evidence that the rise of temperature is dependent on an inability of the body to mobilize its water reserve. It is true that the heat loss in vaporization of water is low when compared with the enormously increased heat production of a chill, but it never falls far below its average normal relation to the total elimination and as in the two cases just cited may rise considerably above it.

The Influence of Body Temperature on Heat Production.—In discussing the conditions in the period following a chill, it was emphasized that the heat production remained from 20 to 40 per cent. above the normal level after shivering had ceased. It was also remarked

20. Soderstrom, G. F., and Du Bois, E. F.: Clinical Calorimetry, Paper 25. The Water Elimination Through Skin and Respiratory Passages in Health and Disease, Arch. Int. Med. **19**:931 (June) 1917.

Fig. 9.—Relationship of basal metabolism to temperature in the fever following the injection of foreign protein. Ordinates represent rectal temperature in degrees centigrade, abscissae the metabolism expressed in percentages of the average normal. Each dot represents an experimental period in the calorimeter.

Fig. 10.—Relationship of basal metabolism to temperature in malarial fever.

that this was the usual finding in conditions of increased body temperature. Work on typhoid fever, tuberculosis and malaria has demonstrated that rise in body temperature is accompanied by increased heat production and that the increase corresponds to the degree of fever. Figure 9 shows the relation of heat production to the degree of body temperature after the injection of foreign protein expressed by the method utilized by McCann and Barr²¹ in tuberculosis. The ordinates show the rectal temperature in degrees Centigrade. The abscissae show the level of the metabolism in percentage of the average normal. The line 90 means 10 per cent. below the average; 150 means 50 per cent. above the average. Each dot represents a calorimetric observation. Of course, it is necessary to leave out the shivering periods. It is possible that some of the results in the very high temperature following the chill are slightly affected by previous severe muscular exercise. Figure 10 demonstrates the relationships during the fever of malaria. In Figure 11 are grouped in one chart all of the fevers studied. The continued diagonal line is drawn from statistical calculations and the dotted lines are placed to represent divergencies of 10 per cent. in this average. Out of the total of 137 experiments in various fevers, 82 per cent. come within 10 per cent. of the average. In other words, the percentage variations in the metabolism for a given temperature are slightly greater than a similar group of normal individuals.

Most of the patients whose metabolism is very high for the degree of temperature were typhoid or malaria patients with a high level of protein metabolism. Most of those with low basal metabolism were cases of tuberculosis with a normal protein metabolism. We know that protein increases the metabolism through its specific dynamic action and this may explain the difference between the groups of patients. The ingestion of a large protein meal does not increase the heat production in typhoid where the protein metabolism is already high, but it does cause a striking increase in tuberculosis where the protein metabolism is at a much lower level. While the increased protein metabolism seems to be a factor in explaining differences between the various fevers we believe that it is outweighed by another and simpler factor.

The surprising uniformity of results expressed in Figure 11, suggests that we are dealing with a law of the velocity of chemical reactions enunciated by van't Hoff.²² For ordinary temperatures the van't Hoff law can be expressed as follows: "With a rise in

21. McCann, W. S., and Barr, D. P.: Clinical Calorimetry, Paper 29. The Metabolism in Tuberculosis, Arch. Int. Med. **26**:663 (Nov.) 1920.

22. van't Hoff, J. H.: Studies in Chemical Dynamics. Revised by E. Cohen, Translated by T. Ewan. Easton, Pa. Chemical Publishing Co., 1896.

Fig. 11.—Relation of basal metabolism to temperature in six different fevers. The continuous line shows the average and the dotted lines are drawn to represent metabolism 10 per cent. above and 10 per cent. below the average.

temperature of 10 C. the velocity of chemical reactions increases between two and three times." In other words, the temperature coefficient is usually between 2 and 3. This means an increase of from 30 to 60 per cent. for the three degree rise from 37 C. to 40 C. Virtually all of the fever experiments are within these limits and the average line shows a temperature coefficient of 2.3.

Van't Hoff and Kanitz²³ give the temperature coefficients which show the rate of increase in a number of chemical reactions with an equal rise in temperature. If we plot these in exactly the style of the

Fig. 12.—The lines in this chart represent a number of typical chemical reactions taken from van't Hoff and Kanitz. The slope of the lines shows the increase in the rate of the reactions as the temperature is raised. Note that the lines correspond closely to those which represent the total oxidations in the human body.

fever patients (Fig. 12) we note that the lines have approximately the same slope. In other words, the reactions in a fever patient respond to a rise in temperature in a manner which resembles closely the chemical reactions in the test tube suspended in a water bath.

There is a tremendous gap between the simple reactions in the test tube and the complex oxidations in the diseased human body and we should hesitate to compare them were it not for the large number

23. Kantiz, A.: Temperatur und Lebensvorgänge in Biochemie in Einzeldarstellungen: Heft 1. Gebrüder Bornträger, 1915, Berlin.

of biologic reactions which show temperature coefficients between 2 and 3. Van't Hoff calls attention to the rate of carbon dioxide elimination in plants which show a coefficient of 2.5. Kanitz gives a long list of similar coefficients for plant respiration, rate of isolated hearts, contraction of smooth muscle and the metabolism in cold blooded animals.

SUMMARY AND CONCLUSIONS

1. Eight calorimeter experiments have been made on subjects after the intravenous injection of proteose and of typhoid vaccine. In five of these it was possible to observe the phenomena of chills.

2. With the onset of a chill there is a sudden increase of from 75 to 200 per cent. in heat production due, in part, to the shivering. At the same time, there is almost no rise in the heat elimination. This discrepancy between production and elimination causes the storage of a large amount of heat within the body. After the chill there is a short period of level temperature when the heat production and heat elimination are equal and both are from 20 to 40 per cent. above the basal level. Following this, as the temperature falls, there is usually a steady decrease in heat production until it reaches the normal level. The heat elimination, on the other hand, increases still farther, thus getting rid of the stored heat. During the falling temperature there is never as large a discrepancy between elimination and production as during the chill.

3. The respiratory quotient tends to be high during the chill, indicating the rapid combustion of the glycogen stores of the body. After the chill, the quotient falls steadily.

4. By means of a comparison of the heat production and heat elimination, it is possible to determine the temperature changes of the body as a whole and compare them with the changes in rectal temperature. The rectal temperature indicates, in a general way, changes in average body temperature, but it is possible to have a rise in rectal temperature while there is a fall in the average body temperature. The opposite is also true.

5. The heat lost in the vaporization of water from the skin and lungs bears a fairly constant relationship to the total heat elimination but has no relationship to the heat production during rapid changes in temperature. Study of the water elimination in fever affords no evidence that the body is unable to mobilize water for heat elimination. Fever should not be attributed to failure in the function of water elimination.

6. Observations in this and in other fevers has demonstrated that rise in body temperature is accompanied by increased heat production the amount of which corresponds to the degree of fever. It is found

that this increase follows van't Hoff's law, which may be stated as follows: "With a rise in temperature of 10 C., the velocity of chemical reactions increases between two and three times."

7. The phenomena of the chill following intravenous injection of proteose or vaccine are strikingly similar to those of the malarial paroxysm, the method of temperature regulation being almost identical.