CLINICAL CALORIMETRY

TWENTIETH PAPER

THE EFFECT OF CAFFEIN ON THE HEAT PRODUCTION *

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The object of this research was to determine the effect of a single large dose of caffein on the respiratory metabolism of normal individuals.

The earliest work on the effect of this drug on the gaseous exchange, so far as we have been able to discover, was that of Hoppe¹ in 1857. He found some increase in the carbon dioxid output after taking caffein, but the conditions of his experiments are open to criticism. He was followed two years later by Smith² who studied in a masterly way nearly every aspect of respiration, including the effect of tea, coffee, etc. His technic, so far as one can judge from the description, was excellent. His apparatus was of the open circuit type, the subject breathing through a mask and valves. The inspired air went first through a dry meter and the expired air first through a Woulff bottle, containing pumice stone saturated with sulphuric acid, then through a gutta-percha box having a series of compartments in which the air was exposed, over a large surface, to concentrated potassium hydrate. Next, it was passed through a second Woulff bottle with sulphuric acid, the carbon dioxid was determined by the gain in weight of the absorbers, exactly as is done with the modern calorimeter. The total ventilation of the lungs, the evaporation of moisture from the lungs, the respiration rate and pulse rate were the other factors studied. The oxygen, of course, was not obtained. After taking from 50 to 100 grains of black or green tea leaves, or half an ounce of strong coffee, a rise in the carbon dioxid output was invariably found with

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1. Hoppe: Ueber die Wirkungen des Coffein, Deutsch. Klin., 1857, **9**, 181.

2. Smith, Edward: Experimental Inquiries Into the Chemical and Other Phenomena of Respiration and Their Modifications by Various Physical Agencies, Philosophical Transactions, London, 1859, **149**, 681.

several normal subjects. A very large number of experiments were performed. The rise was anywhere from 15 to 30 per cent. and the maximum usually occurred within an hour from the time of taking the drug. An increase in the ventilation of the lungs of similar proportion was also found. The respiratory rate was sometimes increased, sometimes decreased. The pulse was usually slightly accelerated.

The next extensive study of the effect of caffein on the metabolism, so far as we are aware, is that of Reichert³ in 1890. This observer worked with dogs, his apparatus being a simple type of water calorimeter. The method of direct calorimetry alone was used. His work may be subject to some criticism, for the dogs were tied down and occasionally struggled. The results of his normal control experiments sometimes differed rather widely, but the faults were remedied to some extent by the very large number of experiments made. The caffein was given subcutaneously. A basal hour was secured first and the dogs were then observed for five hours after receiving the drug. Three series of experiments were performed. In the first series the dose was 0.035 gm. per kg. Five experiments were made. The average increase in heat production was 38.6 per cent. Heat elimination was also increased, but in relation to production was inconstant. In three experiments heat elimination was in excess; in the other two it was not. In the second series, 0.07 gm. per kg. were given. The average increase in heat production was 43.6 per cent. The maximum was reached in two experiments during the first hour after administering the drug; in three, during the second hour. In all the experiments of this series, heat production was in excess of elimination during the first hour, and in three, in excess during the subsequent hour. More heat was eliminated than produced during the remaining hours. In the third series, 0.105 gm. per kg. was given. (The lethal dose was from 0.15 to 0.20 gm. per kg.). In this series there was an average increase in heat production of 71.4 per cent. In all the experiments heat production was in excess of elimination in the first hour and in three also in the second hour. In summing up, Reichert says, "These results show beyond possible doubt that caffein increases heat production, and as a corollary, increases destructive tissue metamorphosis."

More recently, Edsall and Means⁴ reported experiments on the effect of caffein on two normal men. In one, after 0.324 gm. of caffein

3. Reichert, E. T.: Action of Caffein on Tissue Metamorphosis and Heat Phenomena, *New York Med. Jour.*, 1890, **51**, 456. For a description of his apparatus see Heat Phenomena in Normal Animals, *University Med. Mag.*, Philadelphia, 1890, **2**, 173, 225, 345.

4. Edsall, D. L., and Means, J. H.: Effect of Strychnin, Caffein, Atropin and Camphor on the Respiration and Respiratory Metabolism in Normal Human Subjects, *THE ARCHIVES INT. MED.*, 1914, **14**, 897.

CAFFEIN. DATA OF—

Subject, Date, Weight, Surface Area, Linear Formula	Period	End of Period	Carbon Dioxid, Gm.	Oxygen, Gm.	R. Q.	Water, Gm.	Urine N per Hour, Gm.	Indirect Calo- rimetry, Cal.	Heat Elimi- nated, Cal.
Case 1..... (E. F. D. B.) 4/12/16 76.5 Kg. 1.94 Sq. M.	Prelim.	11:32							
	1	12:32	25.4	22.7	0.81	31.5	0.502	75.5	82.4
	2	1:32	24.7	22.7	0.79	32.7	0.502	75.3	82.0
Av. basal.....								75.4	
	3	2:32	27.8	25.7	0.79	37.8	0.688	84.7	87.4
	4	3:32	25.6	23.5*	0.79	37.1	0.688	77.5	82.4
Av. after caffein									
E. F. D. B.	Prelim.	11:07							
4/25/16 77.3 Kg. 1.95 Sq. M.	1	12:07	24.4	22.1	0.80	33.3	0.536	73.2	78.9
	2	1:07	27.1	Lost		34.7	0.705	83.5†	82.0
	3	2:07	25.9	Lost		35.7	0.705	78.9†	83.3
	4	3:07	25.8	24.6	0.77	33.8	0.579	80.7	79.5
	5	4:07	26.2	23.7	0.81	34.9	0.579	78.6	81.6
Av. after caffein								80.6	
Case 2 (J. H. M.)..	Prelim.	11:26							
4/21/16 75.3 Kg. 1.89 Sq. M.	1	12:26	24.2	21.9	0.80	32.3	0.524	72.8	81.3
	2	1:26	25.1	23.1	0.79	34.9	0.524	76.4	87.5
Av. basal.....								74.6	
	3	2:26	29.5	26.5	0.81	36.1	0.604	88.1	84.3
	4	3:26	28.9	27.3	0.77	41.2	0.604	89.9	90.0
	5	4:26	31.5	29.9	0.77	42.2	0.618	98.4	89.7
Av. after caffein								92.1	
Case 3 (J. C. F.)...	Prelim.	11:39							
4/27/16 64.3 Kg. 1.75 Sq. M.	1	12:39	23.6	21.2	0.81	26.8	0.592	70.4	70.5
	2	1:39	25.9	22.7	0.83	28.6	0.592	75.7	77.4
Av. basal.....								73.1	
	3‡	2:42	26.3	24.7	0.78	36.9	0.631	81.1	87.0
	4§	3:39	25.8	22.8	0.82	41.7	0.516	76.1	81.8
	5	4:39	26.6	23.3	0.83	34.3	0.414	78.0	76.6
Av. after caffein								78.4	
Case 4 (J. C. A.)...	Prelim.	11:10							
4/29/16 60.2 Kg. 1.64 Sq. M.	1	12:10	22.3	19.1	0.85	29.6	0.546	64.0	70.3
	2	1:10	22.8	19.2	0.87	29.6	0.546	64.5	72.4
Av. basal.....								64.3	
	3	2:10	25.4	21.9	0.84	32.6	0.546	73.4	75.2
	4	3:10	26.4	24.6	0.78	38.4	0.546	81.2	81.6
	5	4:10	22.6	20.2	0.81	33.4	0.546	66.9	73.1
Av. after caffein								73.8	

* Small leak found in blower this hour.

† Calculated from CO₂, R. Q. assumed to be 0.79.

‡ 63-minute period.

§ 57-minute period.

—CALORIMETER EXPERIMENTS

Direct Calorimetry Calories	Rectal Temp., C.	Average Pulse	Work-Adder, Cm.	Non-protein R. Q.	Per Cent. Calories from			Calories per Hour		Remarks
					Protein	Fat	Carbo-hyd.	Per Kg.	Per Sq. M.	
.....	36.9	62								
80.8	36.8	56	9	0.82	..	..	..		38.9	Basal; very quiet; on right side
81.0	36.8	58	24	0.79	..	..	..		38.8	Basal; very quiet; on back
.....					18	56	26	0.99	38.8	Caffein, 0.65 gm. at 1:33 p. m.
89.1	36.9	56	22	0.78	22	58	20		43.6	Very quiet
81.5	36.9	55	14	0.79	24	55	21		40.0	Very quiet
.....					..	..	..		41.8	
.....	86.9									
71.5	36.8	56	28	0.80	19	54	27	0.95	37.5	Basal; quiet
78.5	36.8	55	30		..	..	..		42.8	Caffein, 0.65 gm. at 12:08 p. m.; quiet
86.3	36.9	60	13		..	..	..		41.0	Very quiet; on right side
79.8	36.9	55	11	0.76	19	67	14		41.4	Very quiet; on back
82.4	37.0	56	21	0.81	20	53	27		40.3	Quiet
.....					..	..	..	1.04	41.4	
.....	36.9									
71.6	36.7	59	26	0.80	..	..	..		38.5	Basal; fairly quiet
83.4	36.7	55	30	0.79	..	..	..		40.4	Basal; fairly quiet
.....					19	57	24	0.99	39.5	Caffein, 0.65 gm. at 1:27 p. m.
90.4	36.8	57	21	0.81	18	53	29		46.6	Fairly quiet
92.6	36.9	62	32	0.76	18	67	15		47.5	Fairly quiet
96.5	37.0	77	39	0.76	17	68	15		52.0	Fairly quiet
.....					18	63	19		48.8	
.....	36.3									
71.2	36.3		19	0.81	22	50	28		40.2	Basal; very quiet
78.0	36.4		45	0.84	21	43	36		43.3	Fairly quiet; reading
.....					22	46	32	1.14	41.7	Caffein, 0.54 gm. at 1:43 p. m.
81.5	36.3		33	0.77	22	62	16		46.4	Very quiet
73.8	36.2		33	0.83	17	49	34		43.5	Very quiet; slept 25 minutes
77.0	36.3		32	0.84	14	48	38		44.5	Very quiet
.....					18	53	29		44.8	
.....	36.8									
75.9	36.9	66	18	0.86	..	..	..		39.0	Basal; very quiet
73.6	36.9	65	9	0.89	..	..	..		39.3	Basal; very quiet
.....					..	..	..	1.07	39.1	Caffein, 0.525 gm. at 1:11 p. m.
74.0	36.9	61	21	0.85	..	..	..			Fairly quiet
80.6	36.9	59	46	0.77	..	..	..		49.5	Fairly quiet
67.7	36.8	59	18	0.82	..	..	..		40.7	Very quiet
.....					23	33	44	1.23	45.0	

¶ Average of whole experiment.

sodium salicylate, given subcutaneously, there was an average rise of 10.6 per cent. in the metabolism, as measured by indirect calorimetry. The maximum of 13.9 per cent. was reached in the first hour. With the other subject there was an average rise of 3 per cent. and a maximum of 5.7 per cent. after 0.39 gm., given in the same way.

Higgins and Means⁵ obtained similar results. In one normal subject, after 0.32 gm. of caffein sodium benzoate subcutaneously there was an average rise of 13.8 per cent. in the indirect calorimetry. The maximum rise of 15.4 per cent. occurred within the first hour. In another normal subject, 0.32 gm. of the same drug was given subcutaneously and was followed by an average rise of 4.5 per cent. and a maximum of 7.2 per cent., which occurred during the second hour.

In neither Edsall and Means' nor in Higgins and Means' experiments was there any consistent change in the respiratory quotient after the drug; in other words, the proportion of fat, carbohydrate and protein utilized showed no regular deviation from the normal.

METHODS OF EXPERIMENTS

Five calorimeter experiments on four normal men were carried out in precisely the same way as already described in the preceding papers of this series.⁶ The surface area of all the subjects was determined by the so-called "Linear Formula," described in Papers 5, 9 and 10. The calories derived from protein were calculated from specimens voided between the hours of 8 a. m. and 5 p. m.

The caffein was taken in the form of the pure alkaloid dissolved in water. A tumbler containing the caffein dissolved in 300 c.c. of water at room temperature was placed in the calorimeter when the subject entered. After a preliminary period and one or two hours of observation of the subject's normal basal metabolism, he was told to drink the mixture and was allowed to follow it with a little pure water. After the taking of the drug the observation was continued for three hours, except in one experiment, when the third hour was omitted.

The subjects were studied in the morning hours at complete rest, fourteen to eighteen hours after the last meal. They were not allowed to take coffee or tea for the twenty-four hours previous to the test.

The data of all the experiments are given in the accompanying table.

DESCRIPTION OF SUBJECTS OF EXPERIMENTS

CASE 1.—E. F. D. B., man, aged 34, height 178 cm., physician. For history see Fourth Paper of this series. Since last year he has been in good health; has taken very little exercise since September, 1915. Takes one medium-sized

5. Higgins, H. L., and Means, J. H.: Effect of Certain Drugs on the Respiration and Gaseous Metabolism of Normal Human Subjects, *Jour. Pharmacol. and Exper. Therap.*, 1915, **7**, 1.

6. Papers 1 to 8: *THE ARCHIVES INT. MED.*, 1915, **15**, 793-944; Papers 9 to 17: *Ibid.*, 1916, Part 2, **17**, 855-1059.

cup of coffee at breakfast and occasionally tea in the afternoon, or a small cup of coffee after dinner. Is kept awake by coffee or tea taken after 1 p. m. Tobacco, moderate. Alcohol, occasionally in small amounts.

CASE 2.—J. H. M., man, aged 31, height 177 cm., physician. Measles, mumps, scarlet fever and chickenpox in childhood; a bronchopneumonia at 26 and paratyphoid at 28; otherwise, has always enjoyed good health. Takes exercise only spasmodically, but leads a fairly active life.

Takes one cup of coffee in the morning about half the time, a small cup of coffee after dinner about twice a week, one or two cups of tea in the afternoon about four times a week. One demitasse will not keep him awake; a large cup of coffee in the evening will. Tobacco, moderate. Alcohol, occasionally in small amounts.

CASE 3.—J. C. F., man, aged 23, height 178 cm., chemist. Pleurisy and pneumonia at 6; scarlet fever at 13; occasional sore throat. In good health except for slight nasal obstruction. Exercise: walks three to four miles a day.

He takes a cup of coffee at each meal and sometimes a cup late at night without being kept awake. Tobacco, three to five cigars a day. Alcohol, none.

CASE 4.—J. C. A., man, aged 26, height 175.2 cm., physician. Scarlet fever nine years ago; catarrhal jaundice five years ago; in good health since. Leads a sedentary life, but always takes some exercise.

Takes two cups of coffee a day; no tea. Even large quantities of coffee in the evening never keep him awake. Tobacco, ten cigarettes a day. Alcohol, occasionally in small amounts.

DISCUSSION OF RESULTS

The Basal Metabolism After Giving Caffein.—This was increased in each experiment. The dose given, 8 to 10 grains, approximately 8.6 mg. per kg. of body weight, is considerably larger than the usual therapeutic dose. In all five experiments there was a rise in the basal metabolism (indirect calorimetry). This rise varied from the minimum of 11.3 per cent. with J. C. F., to the maximum of 31.6 per cent. with J. H. M. The highest average rise was that of J. H. M., 23.5 per cent., and the lowest that of J. C. F., of 7.4 per cent. In three experiments, both those on E. F. D. B. and that on J. C. F., the maximum rise occurred in the first hour after receiving the drug. In the experiment on J. C. A., the maximum rise occurred in the second hour, and that in J. H. M. in the third hour. In none of these experiments had the metabolism returned to the basal value when the observation was discontinued. The increments in the metabolism obtained in this series of experiments are definitely greater than those obtained by Edsall and Means and by Higgins and Means when using much smaller doses of the drug. The rises in the basal metabolism of the present experiments are shown graphically in the accompanying figure.

As one looks over the enormous literature on the various actions of caffein, one gets the impression that the numerous contradictory statements are not necessarily due entirely to faulty observation, but possibly because the action of caffein on any given function is extremely variable, often diametrically opposite, in different individuals, and in the same individual with varying dosage. Nevertheless, the present

series of experiments, together with those in the literature, show that an elevation in the basal metabolism is a very frequent action, although its intensity varies considerably in different individuals. In general, there seems to be a larger rise with larger doses.

The Respiratory Quotients.—These show no consistent change in either direction after the drug had been taken.

The Methods of Direct and Indirect Calorimetry.—These agree closely in the hours following the taking of caffeine. The total calories as measured by the former method in the hours following the drug were 1,230.3. This is within 1 per cent. of the total of 1,218.0 calories as measured by the method of indirect calorimetry. This agreement of two absolutely independent methods is unusually close, and it confirms the technical accuracy of the findings. The drug had little effect on

Results shown graphically. Columns represent calories per hour as measured by indirect calorimetry. Arrows indicate point at which the caffeine was taken. The topmost lines show the respiratory quotients.

the body temperature and the differences between heat elimination and heat production are such as would be found in experiments on normal controls.

The agreement between the methods of direct and indirect calorimetry in the basal hours before the drug was taken is not very close. The direct method gives a total of 687.6 calories; the indirect, 647.8 calories. The method of direct calorimetry is seldom very satisfactory in the first hour of an observation, and these one- or two-hour basal experiments are not long enough to balance up the inequalities. With longer experiments on normal controls the agreement is within a fraction of 1 per cent., as has been shown in previous papers.

The Elimination of Water from Skin and Lungs.—This was increased, after taking the caffeine, in every experiment. This was greatest in the case of J. C. F., being 36 per cent. and least in the second

experiment on E. F. D. B., when it was but 5 per cent. The average percentage of calories lost in the vaporization of water during the basal hours was 24.1 per cent.; after taking the caffein the average was 26.3 per cent. The drug affects but slightly the mechanism by which the body dissipates heat in response to an increased heat production.

Nitrogen Elimination.—The total nitrogen in the urine showed a rise after taking caffein in each experiment except that on J. C. A., when the data were not obtained. This rise was greatest in the first experiment on E. F. D. B., 37 per cent., and next greatest in the second experiment on the same subject, 31 per cent. It was least in the case of J. C. F., 6 per cent. J. C. F. likewise had the least rise in basal metabolism, but E. F. D. B. did not have the greatest. This increase might have been merely the washing out of nitrogenous bodies as a result of the caffein diuresis.

The Pulse Rate.—This showed sometimes a slight rise, sometimes a slight fall, or else no change at all after the subject received the drug.

SUMMARY

An increase of from 7 to 23 per cent. in the basal metabolism was found in four normal subjects after receiving 8 to 10 grains of caffein alkaloid (8.6 mg. per kg. of body weight). After taking the drug there was no significant change in the pulse rate, in the respiratory quotient, in the proportions of the various foodstuffs metabolized, or in the percentage of heat lost in the vaporization of water. The independent methods of direct and indirect calorimetry gave results which agreed within 1 per cent.

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