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Mechanism of Pyrogen Induced Fever.*

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The fever which occurs in several animal species following the injection of certain bacterial products[1-3] has been observed to be associated with an increase in oxygen consumption.[4-8] Quantitative study of heat exchange in man during this "pyrogenic reaction" has revealed that during the "chill phase" there is a substantial increase in heat production with no change in heat loss.[4] Simulated shivering in a normal man has been shown to produce the same magnitude of increase in heat production as observed during the pyrogenic chill.[9] However, in contrast to the pyrogenic reaction, a simultaneous increase in heat loss was observed, so that only a slight fever developed. It may thus be inferred that interference with heat loss is an important factor in the production of pyrogenic fever, and that demonstration of its alteration during this reaction is masked by the appearance of increased heat production due to activity of the skeletal muscles in the process of shivering. Consequently, it is of interest to know if a febrile response to pyrogen can occur in an animal incapable of increased heat production by voluntary muscle movement, and if so, to determine under these conditions the nature of the alteration in heat exchange. Thus, the pyrogenic reaction has been studied in the curarized dog.

The pyrogenic substance employed in the present studies is a purified material obtained from *Pseudomonas aeruginosa*† and provided

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† Chemical properties of this substance will be described in a forthcoming paper by Dr. L. G. Ginger and coworkers.

TABLE I.
Influence of Pyrogen on Heat Exchange in Curarized Dogs.

Exp. No.	Wt, kg	Avg pre-febrile heat production and loss (cal./min.)	Period of rising temperature: Duration (min.)	Temp. increment (°C)	Change in avg: Heat loss (%)	Change in avg: Heat prod. (%)	Fraction of stored heat due to alteration of: Heat loss (%)	Fraction of stored heat due to alteration of: Heat prod. (%)
1	7.3	.210	120	1.52	—29.0	+ 7.6	79.2	20.8
2	8.2	.254	135	1.28	—21.3	+ 3.0	87.6	12.4
3	10.5	.306	166	2.86	—33.7	+15.4	68.7	31.3
4	10.5	.424	170	1.40	—14.6	+ 4.0	77.9	22.1
5	8.2	.250	110	1.44	—29.6	+ 6.0	83.2	16.8
6	6.8	.253	140	1.34	—16.6	+ 4.7	77.8	22.2
7	14.5	.485	70	1.12	—35.9	+ 3.9	90.1	9.9
8	11.4	.335	240	2.35	—14.3	+13.4	51.4	48.6
9	6.3	.250	80	0.84	—13.2	+ 8.8	59.9	40.1
10	10.1	.306	100	1.66	—41.5	+ 3.9	91.4	8.6
11	11.1	.426	130	2.84	—25.8	+21.4	54.8	45.2
12	11.8	.491	110	1.50	—22.6	+ 4.7	82.8	17.2
13	10.0	.291	180	1.90	—22.7	+ 7.6	74.9	25.1
14	15.0	.491	200	1.55	—13.6	+ 5.1	74.0	26.0
Mean					—23.9	+ 7.8	75.3	24.7
Stand. Dev.					± 9.0	± 5.0	±12.0	±12.0

for us‡ in the form of a standard concentrate. This material will produce, on first intravenous injection, a febrile response in the normal dog in doses of 2-3 μg/kg. In doses of 25-50 μg/kg this material produced, after a latent period of 18.8 ± 7 minutes, a rise in rectal temperature of 1.77 ± 0.5°C in 14 non-curarized dogs.

For the studies performed on the curarized dog, crystalline *d*-tubocurarine§ was employed. The initial paralyzing dose was 1-1.5 mg/kg given intravenously, and subsequent curarization was maintained by the hourly intramuscular injection of 0.5 mg/kg. Artificial respiration was maintained in these animals by means of a Starling-Palmer pump adjusted to give a ventilation-oxygen consumption ratio of approximately 20. In order to insure a relatively painless and yet airtight connection between the dog and an oxygen filled spirometer, an endotracheal airway with an inflatable cuff was employed. Carbon dioxide was removed from this closed system by soda-lime and water vapor by calcium chloride. To insure that inspired air was relatively dry, light weight oil, rather than water, was employed in the spirometer. Oxygen consumption from the spirometer was continuously measured. Continuous rectal temperatures were obtained by means of a recording resistance thermometer.

With room temperature held at 27 ± 1°C these curarized animals maintain a very constant rectal temperature in the neighborhood of 38.5-39°C and a very constant oxygen consumption at an average of 70 ± 21 cc per minute.

After a control period of 1-2 hours, the

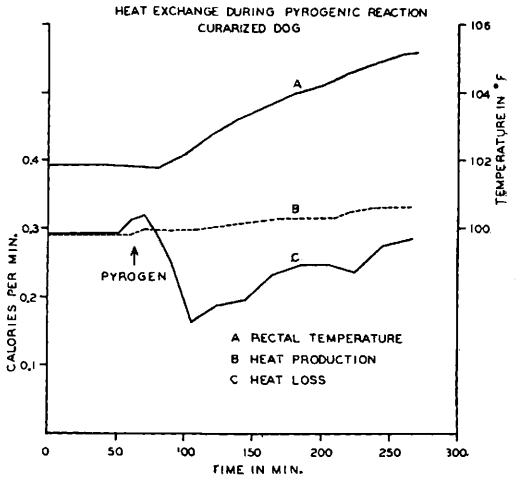

FIG. 1.

‡ Through the courtesy of Dr. N. M. Nesset of Baxter Laboratories.

§ Through the courtesy of Dr. R. K. Richards of Abbott Laboratories.

TABLE II.
Time of Occurrence and Magnitude of Maximum Alteration of Heat Exchange.

	Duration of period of:		Maximum alteration of heat exchange			
			Time of occurrence†		Magnitude‡	
Exp. No.	Latency* (min.)	Rising temp. (min.)	Heat loss (min.)	Heat prod. (min.)	Heat loss (%)	Heat prod. (%)
1	14	120	20	65	—54	+10
2	15	135	57	68	—28	+15
3	7	166	30	122	—69	+30
4	20	170	23	98	—43	+ 9
8	25	240	17	197	—63	+19
11	15	130	30	130	—74	+38
12	18	110	22	82	—37	+ 6
13	12	180	10	150	—44	+11
14	21	200	40	160	—21	+ 9
Mean	16.3	161.2	27.7	119.1	—48.1	+16.3
Stand. Dev.	±5	±42	±14	±45	±18	±11

* Time from injection of pyrogen to onset of fever.
† Time from onset of fever.
‡ Per cent of pre-febrile control level.

curarized dogs were injected intravenously with 25-50 μg/kg of the standard pyrogenic material. After an average latent period of 16.3 ± 5 minutes, the rectal temperature began to rise, and over a period of 161.2 ± 42 minutes had risen 1.69 ± 0.6°C. It is thus apparent that pyrogen induced fever is essentially unaltered by prior curarization and that the reaction can occur in the absence of increased heat production due to movement of the voluntary muscles.

The continuous measurement of rectal temperature and oxygen consumption in these animals makes possible continuous estimation of heat production and loss. The dogs were in a fasting state (24 hours) and the observed R.Q. was of such magnitude (approximately 0.80) as to indicate the use of the factor 4.8 as the caloric equivalent of 1 liter of oxygen. By means of this factor, heat production was determined from oxygen consumption during the pre-febrile control period and during the period of rising temperature.

Heat loss, while equal to heat production during the pre-febrile period of constant temperature, becomes equal to heat production minus heat storage during the period of rising temperature. Heat storage is the product of the rise in body temperature and the specific heat of tissue. The accepted figure for specific heat of tissue, 0.83,[9] has been employed to calculate heat storage, and this in turn to calculate heat loss. In this fashion heat loss and heat production have been continuously determined.

It may be observed (Table I) that during the period of rising temperature, following the injection of pyrogen, the curarized dog shows an increase in average heat production of 7.8 ± 5% over the pre-febrile control level. The heat stored during this period exceeded the heat produced, indicating that a reduction in heat loss had occurred. The average heat loss during the period of rising temperature was found to be 23.9 ± 9% less than during the pre-febrile control period. In these animals, therefore, the average fraction of the stored heat due to increased heat production was 24.7 ± 12% while the fraction due to decreased heat loss was 75.3 ± 12%. Thus, the major fraction of the febrile response to pyrogen is, under these conditions, one of reduction in heat loss.

Additional information as to the relative importance of decreased heat loss and increased heat production during the pyrogenic reaction is obtained from consideration of the time of occurrence of these changes in relation to the onset of fever. It may be seen (Fig. 1) that reduction in heat loss corresponds with the onset of the fever and occurs at a time when heat production is essentially unchanged.

The maximum reduction of heat loss occurs early in the course of the fever and heat loss then slowly returns toward the pre-febrile level as the temperature increases. However, the increase in heat production is progressive and is associated with the rise in temperature. The maximum increase in heat production does not occur until near the peak of the rise in temperature.

Data relative to the time of occurrence and magnitude of the maximum alteration of heat exchange is shown (Table II). The average time of occurrence of the maximum reduction of heat loss was 27.7 ± 14 minutes after the onset of the rise in temperature, while the maximum increase in heat production occurred 119.1 ± 45 minutes after the onset of fever. The degree of alteration of heat exchange which occurred in a rather brief period of time is revealed by the magnitude of the maximum reduction in heat loss, the average of which was 48.1 ± 18% below the pre-febrile control level of heat loss. The corresponding elevation of heat production was 16.3 ± 11% above the pre-febrile level.

It is concluded that the mechanism of the pyrogenic reaction is such that it can occur in the complete absence of increased heat production due to activity of the voluntary muscles, as in the act of shivering, and that under these conditions the primary disturbance is one of rapid and marked reduction of heat loss. The observed increase in heat production is of unknown origin. However, the correlation between the per cent increase in average heat production and the increment in rectal temperature is good (correlation coefficient = 0.82) and the regression is such as to indicate that there is a 7.11% increase in average heat production per degree centigrade rise in rectal temperature. It may, thus, be assumed that the increase in heat production under these conditions is due to the increase in temperature, a phenomenon previously described.[10]

It is known that peripheral vasoconstriction occurs coincident with the onset of the pyrogenic reaction.[2,7,11-13] Since the curarized dog, when artificially ventilated, cannot alter heat loss by reducing the rate of evaporation of water from the lungs or alter radiating surface by change in position, it may be presumed that vasoconstriction is responsible for the observed reduction in heat loss.

Summary. Typical pyrogen induced fever occurs under conditions in which increased heat production due to activity of skeletal muscles is not possible. Under these conditions the mechanism of the pyrogenic reaction is one of sudden and marked reduction of heat loss. The slight increase in heat production under these conditions is correlated with the rise in temperature and is assumed to be a consequence rather than a cause of the fever.

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