Effects of Hypoxia on the Course of Induced Fever in Dogs and Monkeys

W. G. KUBICEK, W. D. ANDERSON and W. F. GEBER

From the Department of Physical Medicine and Rehabilitation, University of Minnesota Medical School, Minneapolis, Minnesota

ABSTRACT


Data were obtained in regard to rectal temperature, inspired pO2, circulation, metabolic rate and hematology. Fevers ranged from 39°C to 45°C and inspired pO2 from 25 mm Hg to 83 mm Hg during hypoxia. In control experiments on dogs with normal body temperature hypoxia resulted in a fall in body temperature, blood O2 and CO2 content, while pulse rate, blood sugar, plasma creatinine and hemocrit increased. The main effects of induced fever in these animals breathing air were an increase in pulse rate, plasma creatinine, blood pH, blood O2 content, hemocrit, O2 consumption rate and CO2 production. Blood sugar usually decreased. Blood pressure either remained essentially constant or fell during the most rigorous experiments. Total leucocyte counts indicated a trend toward an increase and differential counts indicated a rise in the proportion of segmental nuclears and a fall in the relative number of lymphocytes. Hypoxia superimposed upon fever resulted in an increase in rectal temperature in 31%, a decrease in 20% and no change in 49% of the experiments, indicating that under certain conditions hypoxia can aggravate a febrile condition by further elevating body temperature. Fever produced observable tissue damage in the heart, intestine, kidney and liver. No tissue damage could be found in the brain or skeletal muscle. In three experiments cardiac index reached a maximum at approximately 43°C rectal temperature and then fell as the temperature was increased.

INVESTIGATIONS concerning the role of oxygen in the metabolic processes have been carried out throughout the history of medicine. Lavoisier (1) in 1780 was one of the first to recognize the correlation between animal heat and oxidation within the body. The studies of Lusk (2) (1928) were a great contribution to the understanding of oxygen utilization in living systems. During the past two decades, commercial and military aviation have stimulated inquiry into the effects of low oxygen tensions in the inspired air upon normal human beings and animals in an environment cooler than body temperature (3). Some research has been directed at the results of fever alone (4-6). The question of the effect of hypoxia combined with fever has attracted the attention of only a few investigators (7-9).

Clinically, the possibility of disturbances in the delivery of oxygen into the blood stream occurs frequently. Pulmonary edema or atelectasis may impair diffusion of oxygen across the alveolar membranes. In poliomyelitis, airway obstruction or paralysis of the respiratory muscles often results in a reduced alveolar pO2. Other diseases reduce the efficiency of the blood oxygen transport mechanism. The physician is frequently faced with these difficulties combined with an elevated body temperature. During hot weather, the problem of hypoxia in the hospitalized patient leads to the question of the possibility of an impaired temperature
Table 1. Average values of effects of hypoxia on (A) normal and (B) febrile dogs

<table>
<thead>
<tr>
<th>Group A, 10 Experiments</th>
<th>Rectal Temp.</th>
<th>Inspired pO₂</th>
<th>Blood Pressure</th>
<th>Pulse Rate/min.</th>
<th>Blood Sugar</th>
<th>Plasma Creatinine</th>
<th>Blood CO₂ Content</th>
<th>Blood O₂ Content</th>
<th>Hematocrit con-</th>
<th>CO₂ Output</th>
<th>O₂ Con-</th>
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<tbody>
<tr>
<td></td>
<td>°C</td>
<td>mm Hg</td>
<td>mm Hg</td>
<td>mg %</td>
<td>mg %</td>
<td>vol. %</td>
<td>vol. %</td>
<td>cc/m³/min.</td>
<td>cc/m³/min.</td>
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<tr>
<td></td>
<td>C 38.9</td>
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<td>77</td>
<td>1.01</td>
<td>44.4</td>
<td>17.1</td>
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<tr>
<td></td>
<td>H 38.4</td>
<td>46</td>
<td>138</td>
<td>136</td>
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<tr>
<td></td>
<td>C 39.4</td>
<td>Air</td>
<td>212/115</td>
<td>56</td>
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<td>18.2</td>
<td>43.3</td>
<td>241</td>
<td>107</td>
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<tr>
<td></td>
<td>F 42.5</td>
<td>200/118</td>
<td>134</td>
<td>64</td>
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<td>Group BIII, 10 Experiments</td>
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<td>18</td>
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C—control values; F—febrile breathing air; H—hypoxia during normal body temperature (group A exps.) hypoxia during fever (group B exps.) (±0.2° considered no significant change). Animal's physical condition during experiment: 1—good; 2—fair; 3—poor but survived; 4—died during or shortly after experiment. Experiment group: A, effects of hypoxia on normal dogs; B, effects of hypoxia on febrile dogs; B1, febrile rectal temperature fell during hypoxia; BII, febrile rectal temperature unchanged during hypoxia; BIII, febrile rectal temperature increased during hypoxia.

Procedure and Methods

Adult monkeys and dogs were used as the experimental animals in this study. The dogs were young healthy adult males weighing 35-45 pounds and the monkeys were adult M. rhesus, tested for tuberculosis. All animals were fasted for approximately 12 hours before the experiment. The animals were lightly sedated with Demerol or Nembutal and restrained with the head enclosed in a sealed hood (12 x 12 x 14 in.) into which a warmed humidified oxygen, nitrogen mixture flowed at a controlled rate adjusted to maintain the CO₂ level in the hood at approximately 1%. A small opening near the top of the hood allowed gas to escape. After the animal had rested quietly in the hood for 30-60 minutes, a control blood sample was withdrawn from the femoral artery in a syringe containing 0.1 cc heparin solution. The amount of blood drawn was 3-5 cc from the monkeys and 20 cc from the dogs. Additional arterial blood samples were obtained during the course of the experiment. To induce hyperthermia in the monkey, radiant heat was used. In the dog, satisfactory eleva-
HYPOXIA AND COURSE OF INDUCED FEVER

Table 2. Average values of effects of hypoxia
ON FEBRILE MONKEYS

<table>
<thead>
<tr>
<th>Rectal Temp.</th>
<th>Inhospired PO₂</th>
<th>Pulse Rate/ min.</th>
<th>Blood Sugar</th>
<th>Hematocrit</th>
<th>Sedimentation Rate</th>
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<td>F</td>
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<td>Air</td>
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<td>Air</td>
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<td>Air</td>
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<td>76</td>
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<td>H</td>
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<td>94</td>
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<td>No. of obs.</td>
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<td>19</td>
<td>17</td>
<td>15</td>
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C—control values; F—febrile breathing air; H—hypoxia during fever (±0.2°C considered no significant change). Animal's physical condition during experiments: 1—good; 2—fair; 3—poor but survived; 4—died during or shortly after experiment. Experiment group: I, febrile rectal temperature decreased during hypoxia; II, febrile rectal temperature unchanged during hypoxia; III, febrile rectal temperature increased during hypoxia.

Rectal temperature was measured continuously by allowing the animal to breathe warmed humidified air at about 44°C, thus preventing heat loss from the tongue and allowing endogenous heat plus radiant heat from an infrared lamp to elevate body temperature. After rectal temperature had reached the desired level, the radiant heat was reduced. In the experiments on dogs the temperature of the gas flowing into the hood was reduced to approximately 40°C. Body temperature was then regulated by adjusting the radiant heat source until a stable febrile rectal temperature was obtained or until a desired rate of rise of rectal temperature was observed. At this point, a second blood sample was taken and then hypoxia was added to the experimental conditions. Hypoxia was induced by decreasing the rate of inflow of air and passing nitrogen into the hood at a rate sufficient to reduce the PO₂ within the hood to the desired value. At the end of 30 minutes of hypoxia another blood sample was taken and the partial pressure of oxygen (PO₂) within the hood was returned to the control conditions. In some cases, after a period of hypoxia, 100% oxygen was passed into the hood in order to save the animal. In most experiments, the body temperature was allowed to rise until the animal expired. In some experiments, the temperature was returned to normal by allowing the animals to breathe dry, cool air and directing electric fans toward the body. Unfortunately, it was not possible to follow the experimental design in all experiments. In all of the experiments, data were obtained for rectal temperature and inspired PO₂. In nearly every case, values were obtained for pulse rate and in about 80% of the experiments data were obtained for arterial blood pressure, metabolic rate and blood chemistry.

Rectal temperature was measured continuously with iron-constantan thermocouples attached to a Leeds-Northrup Speedomax recorder and checked periodically with a mercury thermometer. In dogs the thermocouple leads were inserted approximately 6 inches and in monkeys about 3 inches.

The partial pressure of oxygen was determined with a Beckman model C oxygen analyzer.

Blood pressure was recorded optically with a Statham model P-23 physiological pressure transducer connected to a Heiland G-150 optical galvanometer which was focused on a Waters kymographic recording camera.

In order to determine oxygen consumption rate, the animal's head was enclosed in an airtight hood, described above, into which gas mixtures were passed at a measured rate of flow. Gas flow rate was measured with a rotameter type of gas flow meter. Oxygen and carbon dioxide concentrations were determined with a Scholander micrometer gas analyzer. All gas volumes were corrected to standard conditions. The oxygen consumption rate per square meter of the dogs was calculated using the following symbols (10) and approximate formula:

\[ \dot{V}_{O₂} = \dot{V} \left( F_{1O₂} - F_{2O₂} \right) / m^2 \]

\[ \dot{V}_{O₂} = \text{oxygen consumption in cc/m}^2/\text{min.} \]

\[ \dot{V} = \text{gas flow rate into hood in cc/min.} \]
\[ \begin{align*}
F_{\text{O}_2} &= \text{fractional oxygen concentration of gas flowing into the hood} \\
F_{\text{O}_2, \text{h}} &= \text{fractional oxygen concentration of gas in the hood}
\end{align*} \]

The rate of CO\textsubscript{2} production was calculated by the following formula:

\[ \begin{align*}
Y_{\text{CO}_2} &= \frac{(V F_{\text{CO}_2})}{m^2} \\
V_{\text{CO}_2} &= \text{CO}_2 \text{ production in cc/m}^2/\text{min.} \\
F_{\text{CO}_2} &= \text{fractional CO}_2 \text{ concentration of gas in the hood}
\end{align*} \]

Surface area of the dogs was calculated from the Meeh-Rubner formula (\(10a, 10b\)):

\[ m^2 = 0.112 W^{2/3} \text{ square meters} \]

\[ W = \text{weight of dog in kilograms} \]

The value of \(V\) varied between 5-30 l/min. according to the size of the animal. The rate of gas flow into the hood (\(V\)) was adjusted to provide a drop of about 2% in oxygen concentration between the gas flowing into the hood and the gas leaving the hood with the dog breathing air. When the oxygen concentration was reduced during the hypoxic phase of the experiment by mixing nitrogen with air, the total flow rate of gas into the hood was held constant. In this way, the CO\textsubscript{2} concentration in the hood was held to less than 2% throughout the experiment.

Plasma creatinine was determined by the method of Folin and Wu (11). Blood glucose levels were determined on arterial blood samples by Nelson's modification of the Somogyi method (12).

The Van Slyke-Neil manometric apparatus was used to determine oxygen and carbon dioxide contents in the arterial blood.

The arterial blood pH was determined with a Cambridge Electron-Ray pH meter (Research Model). All pH values were corrected to the rectal temperature of the animal at the time the blood samples were drawn by application of the factor -0.014 pH per degree of pH meter electrode temperature above rectal temperature (13).

Leucocyte counts were made using National Bureau of Standards certified pipettes and a Levey-Hauser counting chamber. Blood smears were stained with Wright's stain and May-Greenwald-Giemsa stain. At least two counts of 100 cells were made from each blood smear.

The hematocrit was determined by centrifuging heparinized blood in a Wintrobe hematocrit tube at 3000 rpm for 30 minutes.

The sedimentation rate of erythrocytes was determined with a Westergren sedimentation tube. Observations were made at 20, 40 and 60 minutes.

In the event of death, the animal was quickly perfused through the left ventricle with saline followed by 10% formalin. Gross examination of tissue was then performed and tissue for microscopic examination was saved from the brain, visceral organs, and skeletal muscle.

Cardiac output experiments were carried out as follows: the animals were anesthetized with pentobarbital sodium and placed on the table with the head enclosed in the hood. A small incision was made in the skin of the neck directly over the jugular vein. The vessel was freed for a distance of approximately 2 cm by blunt dissection, and ligatures placed as far apart as possible. Heparin was given intravenously (1 mg/kg). The distal ligature was not tightened. A small incision was made in the wall of the vein and a no. 8 x-ray catheter with an angle (30 degrees) at the end was placed so that the tip was in the right ventricle as far as it would go. By previously connecting the catheter to a strain gage, the entrance into the ventricle was easily detected. This system allowed either a sampling of blood directly from the right ventricle by simply disconnecting the catheter from the strain gage or a recording of ventricular pressures. Arterial blood pressures were recorded only

\[ \begin{align*}
\text{Table 3. Average Values of Effect of Fever on Dogs and Monkeys (Mean Values)}
\end{align*} \]

<table>
<thead>
<tr>
<th>Rectal Temp.  ( ^\circ \text{C} )</th>
<th>Blood Pressure mm Hg</th>
<th>Pulse Rate/min</th>
<th>Blood Sugar (mg%)</th>
<th>Plasma Creatinine (mg%)</th>
<th>Blood pH</th>
<th>Blood CO\textsubscript{2} Content %</th>
<th>Blood O\textsubscript{2} Content %</th>
<th>Hematocrit</th>
<th>Sed. Rate mm/hr</th>
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<tr>
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<td>1.30</td>
<td>7.47</td>
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<tr>
<td>F 43.2</td>
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</table>

| Monkeys         |                     |                |                 |                     |          |                  |                  |           |                |                    |
| C 38.5          | 227                 | 87             | 7.40            | 38.2                | 11.8     | 40.0             | 8.6              | 11.5     | 3.7            |                    |
| F 46.5          | 287                 | 46             | 7.35            | 46.3                | 11.2     | 45.0             | 11.5             | 3.7      |                |                    |

C=control values, F=febrile breathing air. Animal's physical condition during experiment: 1=good; 2=fair; 3=poor but survived; 4=died during or shortly after experiment.
HYPOXIA AND COURSE OF INDUCED FEVER

Table 4. Mean Values of Total and Differential Leucocyte Counts and Animal's Condition During Fever and Hypoxia in Dogs and Monkeys

<table>
<thead>
<tr>
<th>Animal's Condition, Mean</th>
<th>Total Leucocyte Count/mm³</th>
<th>Eosinophils</th>
<th>Juveniles</th>
<th>Stab Nuclei</th>
<th>Segment Nuclei</th>
<th>Lymphocytes</th>
<th>Monocytes</th>
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<td>42</td>
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Effect of Fever and Hypoxia on Leucocyte Counts in Dogs

Group I, 1 Experiment

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<tr>
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Effect of Fever and Hypoxia on Leucocyte Counts in Monkeys

Group II, 3 Experiments

1.9

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<tr>
<td>F</td>
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<tr>
<td>H</td>
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</table>

C—control values; F—febrile breathing air; H—hypoxia during fever. Animal's physical condition during experiments: 1—good; 2—fair; 3—poor but survived; 4—died during or shortly after experiment. Experiment group: I, febrile rectal temperature decreased during hypoxia; II, febrile rectal temperature unchanged during hypoxia; III, febrile rectal temperature increased during hypoxia. Differential leucocyte count in per cent.

at each blood sample time by the use of another strain gage inserted into the femoral artery. The catheter in the right ventricle was flushed twice with the venous blood before sampling began. Each sample, both venous and arterial, was withdrawn anaerobically over a period of 30 seconds. The oxygen content of both arterial and venous samples was analyzed by the Van Slyke method. Cardiac index (14) was calculated as follows:

Cardiac index = \( \frac{O_2 \text{ consumption in cc/m²/min}}{A-V} \) (A-V) = liters/min

\( A = \text{arterial blood oxygen content in volumes per cent} \)
\( V = \text{venous blood oxygen content in volumes per cent} \)

Results

The results of typical experiments are presented in detail in figures 1 to 6. The average data obtained from 86 experiments on 29 dogs and 16 monkeys are given in tables 1 to 4. Averaging applicable data from these experiments yielded a composite chart of the effects of elevating rectal temperature of dogs from 37°C to 45°C (fig. 7). Average results of three experiments on cardiac output in relation to rectal temperature are shown in figures 8 and 9. Examples of gross and microscopic tissue studies are presented in figure 10.

Control Experiments. Normal body temperature and hypoxia, table 1. In 10 control experiments upon four dogs with normal body temperature hypoxia resulted in a fall in body temperature, blood \( O_2 \) and \( CO_2 \) content while pulse rate, blood sugar, plasma creatinine and hematocrit increased.

Fever Only. In a typical experiment (81, figs. 1 and 2) in order to obtain an estimate of the limits of some of the variables under febrile conditions with the animal breathing air, the dog was lightly sedated with 150 mg of Demerol given in three intramuscular injections during the first 2 hours of the experiment. Blood \( O_2 \) and \( CO_2 \) content, blood sugar, blood \( pH \), plasma creatinine, hematocrit, \( O_2 \) consumption rate, blood pressure, sedimentation rate and rectal temperature were observed over a 6-hour period. The body temperature was allowed to rise until respiration ceased at a rectal temperature of 45.6°C.

The dog was allowed to lie quietly on the table for 1 hour before data were recorded in order to eliminate as much as possible any effects of excitement during the preparations for the experiment. At approximately 5½ hours the rectal temperature had increased from 39.7°C to 42.6°C. Oxygen consumption, plasma creatinine and blood pressure were found elevated at this point. Blood sugar and

4 Individual data obtained from 86 experiments on 29 dogs and 16 monkeys are given in five tables deposited as Document number 5720 with the ADI Auxiliary Publications Project, Photoduplication Service, Library of Congress, Washington 25, D.C. A copy may be secured by citing the Document number and by remitting $2.53 for photoprints, or $1.75 for 35-mm microfilm. Advance payment is required. Make checks or money orders payable to Chief, Photoduplication Service, Library of Congress.
FIG. 1. Blood pressure, pulse rate, hematocrit and oxygen consumption rate in relation to rectal temperature during an increasing fever in a dog breathing warmed humidified air. Critical point at approximately 6½ hr., rectal temperature 43°C (exp. 81).

FIG. 2. Blood oxygen and carbon dioxide content, blood pH, blood sugar, plasma creatinine and oxygen consumption rate in relation to rectal temperature during an increasing fever in a dog breathing warmed humidified air. Critical point at approximately 6½ hr., rectal temperature 43°C (exp. 81).

FIG. 3. Blood pressure, pulse rate, hematocrit and oxygen consumption rate in relation to rectal temperature in a dog made hypoxic while febrile (exp. 15).

FIG. 4. Blood oxygen and carbon dioxide content, blood pH, blood sugar, plasma creatinine and oxygen consumption rate in relation to rectal temperature in a dog made hypoxic while febrile (exp. 15).

blood CO₂ content were depressed. During the next hour (5½-6½ hr.) the rectal temperature increased from 42°C to 43°C. The data indicate that this was a turning point in the experiment. Oxygen consumption had not increased during this period in spite of a rise in rectal temperature. Blood CO₂ and pH had decreased. Hematocrit, blood O₂ content, blood sugar and plasma creatinine were above the previous values at 5½ hours. Throughout this period the animal exhibited episodes of central nervous system impairment characterized by alternate periods of hyperexcitability followed by central nervous system depression with loss of sensory perception and reflexes. During the next 45 minutes (6½-7½ hr.) oxygen consumption fell, blood pressure dropped precipitously to shock levels, blood sugar and pH decreased while hematocrit, blood O₂ and CO₂ content and plasma creatinine increased. At this point rectal temperature had increased to 45.6°C and respiration ceased. The animal was then perfused with 10% formalin through the left ventricle and the brain and other tissues were prepared for microscopic study.

Fever Plus Hypoxia. An experiment in which fever decreased during hypoxia (exp. 15; figs. 3 and 4).

The dog was sedated with 100 mg of Demerol and allowed to lie quietly on the table for approximately 1½ hours before data were collected. Blood O₂ and CO₂ content, blood sugar, blood pH, plasma creatinine, hematocrit, total and differential leucocyte counts, O₂ consumption rate, CO₂ production, blood pressure, pulse rate and rectal temperature were observed over a 6-hour period. At approx-
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Fig. 5. Blood sugar, rectal temperature and inspired oxygen partial pressure in a monkey made hypoxic while febrile. Note rapid increase in fever during hypoxia (exp. 65).

Imately 43/4 hours the rectal temperature had increased from the control value of 39.6°C to 43°C. Oxygen consumption increased from a control value of 265 cc/m²/min. to 458 cc/m²/min. at 4 hours and declined slightly to 400 cc at 43/4 hours. At this time blood O₂ content had increased from the control value of 14.7 vol.% to 16.8 vol.% and hematocrit from 36.2% to 40.6%. Blood CO₂ content had decreased from 43.6 vol.% to 23.0 vol.%.

Plasma creatinine, blood pH and blood sugar were found increased. At 43/4 hours the inspired pO₂ was reduced from 138 mm Hg to 48 mm Hg. At the end of 30 minutes of reduced pO₂ (5½ hr.) rectal temperature had reversed its upward course and decreased from 43°C to 42.3°C. Oxygen consumption declined to 364 cc/m²/min. Blood O₂ and CO₂ content were 5.8 vol.% and 14.6 vol.%, respectively. Blood sugar increased further to 105 mg%. Blood pH decreased to 7.31, plasma creatinine, hematocrit, pulse rate, systolic blood pressure were increased over the prehypoxic period. Diastolic blood pressure fell to approximately control values while systolic blood pressure was increased. At 5½ hours the inspired gas mixture was changed abruptly to 100% oxygen. Of interest here was the abrupt change in the slope of the rectal temperature curve. During the hypoxic period, rectal temperature had been falling. Within 5 minutes after the beginning of 100% O₂ administration (6 hr.) blood pH fell to 7.27 and systolic blood pressure had dropped sharply while the pulse rate remained elevated. Plasma creatinine, hematocrit and diastolic blood pressure were elevated slightly. Blood sugar fell to approximately control level. Blood O₂ and CO₂ content had increased to 20.5 vol.% and 25.6 vol.%, respectively. At 6½ hours, the rectal temperature had increased to 44°C and in order to save the animal the hood was opened to allow the animal to breathe dry room air for cooling of the tongue. In addition, electric fans were directed at the animal’s body in order to reduce body temperature as rapidly as possible. At the termination of the experiment (7½ hr.) rectal temperature had fallen to normal values, oxygen consumption was found to be approximately the same as for the control value, pH was about normal (7.38) blood sugar had fallen to 56 mg% and blood O₂ and CO₂ content were approaching the control levels. Blood pressure, although below the control level, had improved, pulse rate remained elevated and the circulatory system was considered to be in good condition. Plasma creatinine remained elevated at the end of the experiment. The leucocyte counts indicated a rise in immature cells during fever and hypoxia.

In this experiment, the animal was semicomatose during the febrile period with no unusual signs of central nervous system disturbance. At the end of the experiment the animal was ataxic but able to walk back to the cage.

Experiment in Which Fever Increased During Hypoxia (Exp. 65; Fig. 5). An experiment on a monkey made febrile with radiant heat is presented here in order to illustrate the rapid rise in rectal temperature encountered during hypoxia in some of these experiments. Rectal temperature, inspired pO₂, pulse rate, blood sugar, hematocrit, sedimentation rate and total and differential leucocyte counts were observed during this experiment. The animal was sedated with 10 mg of Demerol. Radiant heat produced by the infrared lamps placed at approximately 24 inches from the animal were used to produce fever. Rectal temperature was elevated from a control level of 39.3°C to approximately 40.5°C in 45 minutes. At this point (1½ hr.) the voltage to the infrared lamps was reduced to a level which just maintained the rectal temperature at about 40.5°C. At 5½ hours rectal temperature
had been stabilized and the inspired \( pO_2 \) was reduced to 50 mm Hg. Within 10 minutes, the rectal temperature began to rise sharply and approximately 20 minutes later (5\( \frac{3}{4} \) hr.) had 'spiked' to 41.8°C. At this point, the animal was allowed to breathe room air, the radiant heat was turned off and an electric fan was directed at the animal's body in order to reduce the body temperature and save the animal. Blood sugar fell somewhat during the febrile period and probably had increased during the hypoxic period as indicated by the value obtained shortly after the end of hypoxia. Hematocrit, sedimentation rate and total leucocyte counts increased during the periods of fever only and fever plus hypoxia. Both mature and immature cells appeared in greater numbers during fever and fever plus hypoxia with a slightly larger proportionate rise in the immature types.

In some experiments femoral artery blood pressure tracings provided a record of the performance of the heart as rectal temperature was elevated (fig. 6). In an experiment (80) on a dog breathing air the rectal temperature was increased from the control level of 38.3°C to 44.8°C in a period of approximately 4 hours.

Optical blood pressure tracings indicated the advent of an increased rate of systolic contraction, extra systoles and a generally irregular heart cycle. In spite of these myocardial disturbances, the heart continued to function and maintained an arterial blood pressure above or about equal to control values up to a rectal temperature of 44.8°C. About 20 minutes after the last blood pressure record was taken, respiration ceased, the animal expired and was immediately perfused with formalin through the left ventricle. Post-mortem examination of the heart revealed extensive subendocardial petechiae and ecchymotic hemorrhages in the left ventricle. The right ventricle showed only slight damage.

In order to portray what could be considered an average physiological response to a progressive rise in body temperature in dogs under the conditions of these experiments, composite graphs of some of the variables were obtained from several experiments on different dogs (fig. 7). The pertinent data were averaged at either 1°C or 0.5°C temperature intervals and plotted against rectal temperature. The abrupt change in some of the curves at approximately 42.5°C rectal temperature indicates what was considered a critical point in these experiments. At about this point, in many experiments, this change was obvious from observation of the animal. The respiratory pattern frequently changed from vigorous panting to a slower and deeper respiration. The heart beat usually became irregular and faster with a femoral pulse of poor quality (fig. 6D). Circulatory collapse would usually occur within 30 minutes if the experiment were not abruptly terminated with a rapid reduction in body temperature. The animals frequently exhibited alternate periods of hyper- and hypo-excitability of the central nervous system in response to sensory stimulation by pressure on the foot pad. A statistical analysis of these data was not performed since all dogs could not tolerate the maximum rectal temperature of 45°C. Consequently more data were available for the lower body temperature than for the rectal temperatures above 42°C. At about this point a progressive reduction occurred in the number of animals able to tolerate the stress of further increasing body temperature until only the stronger animals reached a rectal temperature of 45°C.
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Fig. 7. Composite graph of average values of blood glucose, plasma creatinine, hematocrit, blood CO₂ content, blood pH, blood O₂ content and O₂ consumption rate in relation to rectal temperature in dogs subjected to a progressively increasing body temperature.

Fig. 8. Average effects of progressively increasing fever to terminal levels on cardiac index, effective arterial blood pressure, systolic and diastolic pressure, right ventricular pressure and pulse rate in 3 intact anesthetized dogs.

Although more extensive data would have been desirable, a study of the curves for each variable probably provides a fairly accurate picture of some of the physiologic principles involved as rectal temperature was progressively increased over a 4-5-hour period in normal dogs breathing air.

As an adjunct to these experiments, three experiments upon anesthetized dogs were performed with the main emphasis upon cardiac output as rectal temperature was increased from normal to terminal levels. Average values of cardiac index and other variables of these experiments (figs. 8 and 9) followed in general the pattern of response to fever established in the experiments described above. Cardiac index increased with increasing rectal temperature to a maximum value approximately 50% above control values at about 43°C rectal temperature and then started to decline to terminal levels at 45°C rectal temperature. Mean arterial blood pressure and pulse pressure (fig. 8) reached a maximum between 40°C and 41°C rectal temperature and then declined steadily toward terminal values as rectal temperature was increased. Pulse rate indicated an inverse function of the arterial blood pressure with a minimum at about 40°C rectal temperature. Arterial-venous oxygen difference increased only slightly up to a rectal temperature of about 44°C and then rose sharply due primarily to a fall in venous blood oxygen content. Concomitantly arterial and venous blood carbon dioxide content declined to a minimum at 44°C rectal temperature and then increased somewhat at terminal conditions of the experiments. Hematocrit and plasma creatinine increased throughout the experiments while blood glucose fell to approximately 20 mg% at the terminal fever of 45°C rectal temperature. Arterial and venous blood pH, arterial blood oxygen content, and right ventricular pressure remained nearly constant throughout these experiments (fig. 9).

Twenty-nine experiments upon dogs with fever (40-44°C) plus hypoxia (pO₂ = 25-83 mm Hg) resulted in an increase in body temperature in 34%, a decrease in 21% and no change in 45% of the experiments. Thirty similar experiments on monkeys with fever (39-43°C) hypoxia (pO₂ = 34-64 mm Hg) produced an increase in rectal temperature in 27%, a decrease in 20% and no change in 53% of the experiments.

These data indicate that under certain conditions hypoxia can aggravate a febrile condition by further elevating body temperature. Variations in circulatory and metabolic disturbances probably account for the wide range of response of febrile animals to hypoxia. It is of prime importance here to focus attention upon the fact that in 30% of the experiments...
hypothesis did produce an additional rise in body temperature in animals already febrile. In general, as the animal's condition deteriorated, the trend toward a further elevation in body temperature during hypoxia in febrile animals was more consistent.

In many respects the effects of hypoxia during fever were essentially the same as during control experiments. In these experiments fever usually depressed the blood sugar level. Then the addition of hypoxia in most cases elevated blood sugar toward normal. This was true for both dogs and monkeys.

Hypoxia during fever usually resulted in a further rise in plasma creatinine and hematocrit over that observed during fever with the animals breathing air. Hypoxia led to a decrease in blood O₂ and CO₂ content. On the average, oxygen consumption and CO₂ production decreased somewhat during hypoxia in 13 of the experiments on febrile dogs. On the average the studies of the total and differential leucocyte counts during fever and hypoxia indicated a small rise in total count with a relative increase in segmented nucleated and a proportionate decrease in lymphocytes. In some of the more severe experiments a few myelocytes, normoblasts and nucleated red cells were seen (table 4).

**Gross and Microscopic Tissue Changes.**
Examples of the tissue changes seen in the heart, kidneys and intestines of dogs and monkeys following fever or fever plus hypoxia are illustrated. A monkey used in three fever experiments over a 3-week period did not survive the last experiment with a maximum rectal temperature of 43.7°C (exp. 45). Extensive subendocardial hemorrhage was seen in the base of the left ventricle (fig. 10A). Microscopic examination revealed the vascular damage to extend throughout much of the myocardium (fig. 10B). Dilatation of Bowman's space and moderate necrosis of the tubules were frequent findings following experiments of this type (fig. 10C).

In dogs and monkeys subjected to hyperthermia, the most consistent and extensive gross lesions were found in the myocardium and intestine. Subendocardial ecchymosis in the area of the mitral valve and papillary muscles was the usual finding. Hyperemia and in some cases hemorrhage was found in the stomach, intestine and colon (fig. 10D). The liver usually was engorged, and fat, as indicated by Sudan III stain, was present in some cases. In the adrenals, signs of early necrosis were occasionally noted. The spleen and lymph nodes in some cases showed a hypoplasia of lymphatic cells. The brain and skeletal muscle appeared normal in all animals.

The tissues most affected by fever or a combination of fever and hypoxia were 1) heart; 2) gastrointestinal tract; 3) kidney; 4) liver.

In general, no great differences were apparent between the data obtained from dogs or monkeys. However, the monkey hearts were somewhat more sensitive to damage by fever or fever plus hypoxia than the dog hearts.
Hypoxia added to the febrile condition apparently only accelerated the effects of fever on the tissues of these animals. The same type of damage was seen here as in the experiments with fever only. No conclusive evidence could be found of histologically detectable damage to the brain or skeletal muscles.

**DISCUSSION**

One of the objectives in these experiments was to observe the effects of hypoxia upon body temperature during fever. Hypoxia in the febrile dogs and monkeys resulted in either a fall, no change, or a rise in body temperature. The average of these results indicates no change from a statistical point of view. Physiologically these responses to hypoxia in the febrile animals could occur depending upon the individual variations between different animals. A larger number of more precisely controlled experiments are necessary to provide statistically significant data. Attention should probably be focused upon the fact that in 31% of the 59 fever-hypoxia experiments, hypoxia was accompanied by an increase in the febrile body temperature. This observation, if confirmed by other investigators, may be of considerable clinical importance in the management of some febrile conditions and in the operation of aircraft. In terms of human tolerance, the fevers produced in these experiments were higher than ordinarily encountered in human beings. Also the duration of hypoxia was brief compared to the usual hypoxic episodes in human patients. These criticisms need not detract from the principles involved here. Dogs and monkeys apparently have a greater tolerance to hyperthermia than man. Experiments with longer periods of hypoxia of lesser degree were attempted. Due to the labile nature of the fever under these conditions interpretation of the results of mild hypoxia of long duration was difficult or impossible.

The mean values of the fever-hypoxia experiments indicate that as the condition of the animals deteriorated from good to poor the effect of hypoxia upon fever changed from a decrease in body temperature for the control and febrile animals in good condition to no change in the animals in only fair condition and finally in the animals in poor condition hypoxia resulted in an increase in fever.

The probable interpretation of these findings is that in some animals the circulatory system was impaired to such an extent during fever that the additional stress of hypoxia resulted in a decrease in rate of heat removal from the deep tissues while metabolism con-
continued to produce heat at near normal rates, thereby producing an imbalance between heat production and heat removal with a resultant rise in body temperature. Supporting evidence for this view was the altered arterial blood pressure tracings, hemoconcentration and both gross and microscopic indications of tissue damage especially to the vascular system.

The data reported by Ederstrom (15) concerning blood flow measurements in febrile dogs strengthen the views expressed above. Ederstrom found that blood flow to the tongue increased to approximately six times the control value at 42°C and then started to decrease between 42°C and 43°C. This agrees with our findings that a general deterioration of dogs and monkeys started at approximately 42.5°C.

Zander and Mühlemann (16) attached force applicators to the teeth of some of the monkeys used in these experiments in a separate study on the effect of stresses on the periodontal structures. They reported that these systemically stressed monkeys showed signs of altered permeability of the periodontal capillaries and that the intra-alveolar displacement of the roots was more pronounced than in the non-stressed monkeys.

Of interest in these experiments was the fall in blood sugar during fever (17) and the trend toward an elevation during fever plus hypoxia. It should be noted that the increase in blood sugar during hypoxia in the febrile dogs was less than the increase in blood sugar observed during hypoxia in the control dogs. In the fever-hypoxia experiments upon monkeys the results, although more variable, indicate the same general trend in blood sugar changes as the experiments on dogs.

Adrenal gland disturbances may have contributed to some of the observed metabolic changes. Glick and Ochs (18) utilized adrenal glands, taken from some of the monkeys used in these experiments, in a separate study on the cholesterol distribution in adrenal glands of various animals. They found that the stress of combined fever and hypoxia caused depletion of cholesterol ester, mainly from the outer part of the fascicular zone.

The oxygen consumption rate and CO₂ output control values were rather high. This was probably due to a certain amount of excitement and increased muscle tone which persisted in spite of training and sedation of the animals. However, within the limits of the accuracy of the method, the oxygen consumption and CO₂ production values served as an index of metabolic rate. The decrease in metabolic rate during hypoxia was probably due to the observed decrease in respiratory muscle activity and an over-all decrease in muscle tone during this period.

The finding of a lack of demonstrable brain tissue damage in the animals subjected to the conditions of these experiments was of special interest. A distinguishing feature of these studies was the formalin perfusion of the animals immediately after death, thus preventing postmortem autolysis in the brain. Neither neuron degeneration nor damage to the vascular system of the brain could be found in a total of 12 monkey and 10 dog brains examined. Some animals were subjected to two or three experiments with fever and hypoxia and then were placed in their cages for 2–3 weeks to allow time for possible neuron degeneration to take place. No nervous system impairment was apparent for more than 24 hours after the experiments in any of the animals. At the end of the waiting period, the animals were anesthetized with sodium pentobarbital and killed with formalin perfusion through the left ventricle. Other animals used in acute experiments were killed by formalin perfusion at the end of the experiment. None of the brain sections indicated more than normal variations. A final decision in regard to brain tissue changes under the conditions of these experiments should probably be withheld until more extensive studies of this type are available and histo-chemical studies of the brain tissues can be undertaken. Van Fossan and Clark (19) have reported increased postmortem brain lactic acid following hypoxia in rabbits. Alpert et al. (20) observed a rise in plasma lactate during hypoxia. Cerf et al. (21) observed a reversible suppression of spontaneous electrical activity of the vagal lobe, in intact and isolated goldfish brain heated above a critical temperature (37°C) some irreversible alterations in electrical rhythm above 37°C and a preparalytic excitation phase in some experiments. The histological studies reported by Cornwell (22) concerning postmortem changes...
in brain and spinal cord of cats indicated the need for use of the formalin perfusion technique described above.

For certain applications the conclusions to be drawn from these data may be of great interest. The rapidity of the body temperature response to the onset of hypoxia may be of importance in the operation of aircraft flying at supersonic speeds and reaching high altitude very rapidly. Under these conditions the crew could be subjected to a sudden rise in environmental temperature and simultaneously a rapid decline in oxygen tension in the inspired gases. Figure 5 illustrates the rapid inflection upward of the rectal temperature curve of a monkey made febrile with radiant heat and then subjected to hypoxia of the degree and duration possible in supersonic aircrafts of the predictable future.

The fact that the body temperature response of the febrile animals to hypoxia was not consistent suggests the possible necessity for testing prospective crew members of future aircraft for body temperature stability during simultaneous heat and hypoxic stress. Although prophylactic measures can be taken under ordinary conditions, command of the air and space may someday go to the contest-ants best able to achieve the maximum with both man and machine.

The advice and assistance of Dr. Berry Campbell in the histological studies of brain tissues, the aid of Dr. J. H. Sautter and Dr. J. S. Dawson in the analysis of the histological studies of visceral organs and the contributions of Miss Mildred Olson in the preparation of this manuscript are gratefully acknowledged.

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