

FACTORS AFFECTING THE RESPIRATORY QUOTIENT

by

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INTRODUCTION

When food materials are burned, either in vivo or in vitro, there is a constant ratio of the volume of CO_2 produced to the volume of O_2 consumed for each given food stuff. This ratio is known as the respiratory quotient. The respiratory quotient for carbohydrates is 1.00, the average for proteins is about .85, and the average for fats is .707. This constitutes the theoretical range (.707 - 1.00) of the respiratory quotient and all normal metabolism of a combination of these three energy yielding food stuffs in the body results in a respiratory quotient within this range.

The significance of the respiratory quotient has been the subject of comparatively recent and few investigations. Richardson (60) in 1929 reviewed the available knowledge of the respiratory quotient. He defined it as the ratio of the volume of the CO_2 production to the O_2 consumption during the same time period. However, it is now known that CO_2 is not always released at the same rate as it is produced in the body which results in high or low respiratory quotient values. Richardson (60) observed that it was increased by retention or storage in the body of substances of low respiratory quotient, e.g., fat formed from carbohydrates. Decreases were caused by retention or storage of substances of high respiratory quotient. Examples of this storage were, he reported, sugar from protein, sugar from glycerol, keto acids from fat and carbohydrates from fat.

He outlined the factors which affect the respiratory quotient. He reported nothing which influenced the measurement of O_2 . He did, however, report several things which could alter the measured CO_2 production. It was increased by hyperventilation, lactic acid and keto

acids from metabolism, and acid retention in nephritis and uremia, all of which increase the CO_2 release. Factors which could cause a decrease in the measured CO_2 were listed. They were hypoventilation, oxidation of lactic acid and keto acids, excretion of free acid, synthesis of glucose and glycogen from lactic acid and vomiting with loss of HCl from the stomach. He also reported that alkaline therapy and alkalosis could decrease the measured CO_2 release.

Combeare and Pembrey (14), 1926, wrote on the significance of the respiratory quotient. Their only explanation of the respiratory quotients above and below the theoretical range of .707 to 1.00 was that they were due to conversion of fat to carbohydrates and carbohydrates to fat, respectively. Doncheff, et al. (18), in 1935, reported that respiratory quotients below the theoretical of .707 in frogs must be due to experimental error.

Most of the data appearing in the literature on the respiratory quotient appears only incidentally in experiments concerned chiefly with other problems. The review of the literature below outlines the present available knowledge. Little work has been done on the relationship of the respiratory quotient to some factors such as: pCO_2 in inspired air; blood and tissue buffers; body temperature and oxygen consumption.

The present investigation was undertaken as such a study. pCO_2 in inspired air was varied and the response of the animals in altered respiratory quotients, buffering, and CO_2 retention in the body were noted. During the course of the work, interrelationships between respiratory quotient, pCO_2 of inspired air, and metabolic rate were observed. In certain species, it appears that the significance of the respiratory quotient must be partially interpreted in terms of changes in the metabolic rate.

LITERATURE REVIEW

The Respiratory Quotient

The term "respiratory quotient" is commonly abbreviated the R. Q. In further discussion, the abbreviated form may be used for the sake of brevity.

The influence of the amount and types of food intake on the R. Q. has been widely studied. Early observations with the bomb calorimeter indicated that the R. Q. of the energy yielding food stuffs differed. It is not strange, then, that much effort has been expended in studying the effects of diet on the R. Q.

The ingestion of carbohydrates, especially the simple sugars, resulted in an increase in the R. Q. above the resting R. Q. of .825. Bachmann, et al (2), Carpenter (9, 10), Edwards, et al. (22), and Haldi and Bachmann (33) have studied the ingestion of sugars individually, in combination with each other and in combination with other food materials. They observed increases in the R. Q. which differed with different individual sugars, different combinations of sugars, and also with the species of the animals.

The amount of fat ingestion, and also fat storage, have been found to affect the R. Q. A high fat diet was observed (35) to depress the R. Q. below .707, the theoretical level for the oxidation of fats. An adequate explanation of this depression was not possible even in the light of several known factors which decreased the R. Q.: first, production of glycogen from protein; second, production of glycogen from glycerol; and third, ketosis from ammonia formation. Heinbecker (37) found a similar depression in R. Q.'s in a study of Eskimos who lived on a high fat diet. A fat deficient diet resulted in R. Q.'s above

.95 (8). Brooks (7) in studying hypothalamic obesity observed abnormal rises in R. Q.'s after the ingestion of food. Although they did not attribute them to fat metabolism, Carpenter and Trimble (11), reported non-protein R. Q.'s below .71 during fasting and following the ingestion of protein.

Not only the nature of food but also the volume of food intake has been found to affect the R. Q. Dewar and Newton (17) obtained a linear relationship between R. Q. and food intake in mice, i.e., zero food intake resulted in an R. Q. of fat metabolism, maintenance level of intake in an R. Q. of the diet, and an intake above maintenance in an R. Q. above that of the diet. A statistical study of the R. Q.'s of fasting rats (46) also revealed the R. Q. to be near that of fats (.727). The R. Q.'s of fasting rabbits (74) reached a level of .73 in three days.

It was formerly believed that fasting rendered an animal incapable of carrying on proper carbohydrate oxidation. This was believed because some had observed that carbohydrate ingestion after a fast failed to raise the non-protein R. Q. (71). In studying this, Soskin and Mirsky (71), concluded that: first, there was no suppression of carbohydrate oxidation as a result of fasting; second, the low R. Q.'s of fasting probably resulted from an increased gluconeogenesis; and third, the need for re-interpretation of the significance of the R. Q. The present investigation was undertaken in an endeavor to make this re-interpretation. Henry, et al. (39), observed that the fasting R. Q.'s of fowls was below .7 and that carbohydrate ingestion increased the R. Q.'s to near or above unity.

Kleinman (44) studied the effects of temperature upon the R. Q. of cold-blooded animals and observed that R. Q.'s varied directly with

temperature. He suggested that the low R. Q.'s of hibernating warm-blooded animals may be directly ascribed to the influence of low body temperatures; and claimed that R. Q.'s were similar for active and hibernating animals when body temperatures were the same. Hyperthermia has been shown to be accompanied by an increased R. Q. (75).

Studies of the effects of exercise on the R. Q. have shown that: first, O_2 saturation of venous blood was partially responsible for the increase of the R. Q. during recovery from exercise (43); second, sugar ingestion preceding exercise resulted in an elevated R. Q. during exercise (1); and third, that there was no correlation between muscular efficiency and the height of the R. Q. immediately before exercise (34).

The secretions of the pituitary and islets of Langerhans are known to affect the R. Q. R. Q.'s below normal have been observed in depancreatized animals (4, 40), and hypophysectomy has been demonstrated to result in an elevated R. Q. (4, 26, 62).

A reciprocal relationship between the R. Q. and the barometric pressure has been demonstrated (5, 25), and correlated with the course of gaseous exchange in the lungs (23).

The Metabolism of CO_2 and its Effect on the Respiratory Quotient

For many years, it has been known that CO_2 is an end product of normal metabolism in mammals. This knowledge has prompted many investigations concerned with CO_2 and its role in metabolism. With the advent of isotopic carbon as a tracer, these studies have recently increased in number and importance. Some of these studies are reviewed under "Storage of CO_2 " in the discussion section of this thesis. In most studies reviewed here, the R. Q. was not mentioned - the works were concerned with other problems - and so their importance in an understanding of the R. Q.

can only be conjecture. In order to be of real value in an interpretation of the R. Q., many of the works would have to be redone with this in mind.

When Draper and Whitehead (19, 20) discovered in their studies of diffusion respiration that dogs could live when the percentage of CO_2 was sufficiently high to cause a drop in blood pH to 6.7, the study of CO_2 in metabolism was given a new impetus. Spencer, et al. (72), studied the tolerance of dogs to high CO_2 and learned that they could live for as long as 45 minutes while inhaling 40% CO_2 . Many investigators (6, 13, 16, 21, 23, 36, 52, 53, 55, 67, 68, 74) have studied the effects of CO_2 on animals as apparent in physiological responses.

Several studies (15, 21, 30, 41, 49, 50, 63, 64) have been concerned with the effect of CO_2 in the control of breathing. In view of the effect of lung ventilation rate on the R. Q., their works are of obvious interest in an appreciation of the significance of the R. Q. As a reflection on the possible nature of R. Q. deviations in these studies, it is interesting to note the work of Fitzgerald and O'Connor (27) who found that pCO_2 in alveolar air rose with an increase in the R. Q. and vice versa. The CO_2 tension also rose with an increase in CO_2 production and the O_2 uptake by the blood fell with a rise in CO_2 tension.

In the present studies, the pCO_2 of inspired air and duration of exposure were varied in observing the effects of CO_2 on the oxygen consumption and R. Q. Four species of animals were used to test for possible species differences.

CO_2 has also been studied in diving animals (42, 65), altitude (13, 45,) and diffusion respiration (19, 20, 69).

In a study of CO_2 carrying capacity, content and pH changes produced by inhalation of CO_2 , it was important to know the buffer value of blood.

An indirect measure of this has been obtained by use of the Van Slyke gas analysis apparatus. A more direct approach was the determination of the titratable alkali. Several of these studies have been conducted (32, 51) and curves and values are available.

METHODS AND MATERIALS

Mice

Albino mice of both sexes and of several ages were used. The animals were divided into three experimental groups. The animals of two groups ("A" and "B") were placed individually in closed chambers and expired CO_2 allowed to accumulate. Those of the third group (Group "C") were exposed to rebreathing an atmosphere initially high in CO_2 . In Group "A", a mouse was placed in a closed chamber. Consumed O_2 was not replaced nor was produced CO_2 absorbed. Thus, as the animal breathed, CO_2 tension increased and O_2 tension decreased. The chamber contained approximately three liters. Samples were taken at 20 minute intervals and analyzed on a Haldane-Henderson gas analysis apparatus. A fan was used to mix the air before sampling. The mice were exposed for a two hour period in this chamber.

Animals of the second group of mice (Group "B") were placed in a chamber which contained approximately one liter. The samples were taken at 10 minute intervals and the animals were exposed for one hour. Because of the small size of the chamber a fan was not used to circulate the air. To insure adequate mixing of air, the sampling syringe was flushed rapidly several times just prior to sampling the air for analysis.

Both chambers were fitted with a manometer, thermometer, and burette. Atmospheric pressure was maintained by replacing the sampled air with water from the burette. When an animal was exchanging gases at an R. Q. below unity, a greater volume of O_2 was consumed than CO_2 produced. This difference was also replaced by water. Care was exercised in sampling to make certain that samples were drawn slightly above ambient pressure so as to avoid dilution of the sample with atmospheric air when the syringe

needle was withdrawn from the chamber. Rectal temperatures were taken with a thermometer at the beginning and completion of the experiments.

Animals of the third group of mice (Group "C") were exposed to re-breathing an atmosphere initially high in CO_2 and data were collected as indicated above in Groups "A" and "B". These experiments were made in a three liter chamber.

Rats

Albino rats of both sexes and several ages were used. The animals were divided into two experimental groups. Groups "D" and "E" were treated in the same manner except that different chamber sizes were used. The experiments with rats were conducted as were those with mice described above. R. Q.'s, metabolic rates, and body temperatures were again taken. Two chamber sizes were used containing approximately 3 and 7 liters (Groups "D" and "E" respectively). The air was sampled at 10 minute intervals in the smaller chamber (Group "D") and at 20 minute intervals in the larger chamber (Group "E"). In both chambers, the air was mixed before sampling by rapidly flushing the sampling syringe in the chamber several times. Experiments by the author, however, indicated that the animal's breathing and activity prevented any layering of CO_2 which was measurable with the Haldane-Henderson gas analysis apparatus. The fan and mixing procedure were used to avoid any possibility of layering.

Humans

The researches on humans were divided into four experimental series (Groups "F", "G", "H", and "I"). Subjects in Group "F" were studied for the response to rebreathing a limited volume of air. Subjects in Group "G" and "H" were observed for "recovery" after breathing high CO_2 gas mixtures.

Group "I" was studied for the response of humans to breathing air initially high in CO_2 .

Adult males between the ages of 20 and 35 were used. In Group "F", humans rebreathed air from a large spirometer. The volumes rebreathed varied between 100 and 200 liters. The air was sampled at 10 minute intervals and the volume of inspired air was measured on a dry gas test meter. Minute readings were taken of inspiratory volumes. Respiratory rate was determined by use of a pneumograph and kymograph and time was marked with a signal magnet. Pulse rate and blood pressure by the auscultatory method were taken at five minute intervals.

In Groups "G" and "H", R. Q.'s, metabolic rates, and the respiratory and circulatory responses were observed on the subjects during "recovery" which consisted of breathing atmospheric air at the termination of a period of time during which air was rebreathed, thus increasing percentage of CO_2 . Termination of breathing high CO_2 was at the point when the subject felt the CO_2 tension was intolerable. Subjects in Group "G" rebreathed from a spirometer which contained approximately 100 liters of air and the expired gases were collected in five Douglas bags which were kept separate for sampling and analysis. The length of time gas was collected in each bag depended upon the minute volume of the various subjects. In Group "H", the subjects rebreathed from a Douglas bag which contained 50 or 100 liters. Expired gases were not collected but alveolar samples were taken and analyzed. The effect of recovery on circulation and respiration were again noted.

In Group "I", humans rebreathed gas mixtures initially high in CO_2 . Here, as in the previous experiments, R. Q.'s, metabolic rates, tidal volumes, respiratory rates, minute volumes, pulse rates, systolic, diastolic, and pulse pressures were taken.

Dogs

In Group "J", dogs under surgical nembutal sodium anesthesia were subjected to rebreathing 50 liters of air. The courses of the R. Q.'s and metabolic rates were followed during the research by analysis of gas drawn from the Douglas bag at 10 minute intervals and analyzed on the Haldane-Henderson gas analysis apparatus. At the termination of the experiments, which lasted from 30 to 60 minutes, the "recovery" of the dogs was noted as the animals inhaled atmospheric air and exhaled into Douglas bags. The recovery period studied was from 20 to 60 minutes. The time was largely determined by the condition of the animals. A few dogs had a tendency to aspirate fluids and some of the dogs developed an abnormal panting reflex under the anesthesia which was reflected in excessive minute volumes. Expired gases were collected during tests for the time periods, as the conditions of the dogs permitted: 1-3 minutes, 3-10 minutes, 10-20 minutes, 20-40 minutes, and 40-60 minutes. The volumes were measured on a dry gas test meter and the gas samples analyzed as indicated above.

RESULTS

Storage of CO₂ in the Body

In Table I are shown the volumes of CO₂ stored in the bodies of men, dogs, rats, and mice during rebreathing of air in which the expired CO₂ was allowed to accumulate. These volumes of stored CO₂ were calculated from the data used in obtaining the R. Q.'s and metabolic rates. In the calculations, it was assumed that the type of food materials being burned did not change and that the drop observed in the R. Q. over the course of the experiment was a result of the storage of CO₂. In some experiments, where the initial R. Q. was low, an R. Q. of .85 was used in calculating the amount of stored CO₂. This, of course, gave larger values for stored CO₂ than would have been obtained by calculating from the initially low R. Q. This was done because in some experiments, the CO₂ had accumulated to a level where it could have affected even the initial R. Q. If it was thought that such were possible, an R. Q. of .85 was used. This is the average R. Q. observed in active animals. The data from which the volumes of stored CO₂ were calculated appear in Tables VI, VII, IX, X, XI, and XII. Because quantitative data on oxygen consumption were not sought, the values were all expressed at ambient conditions, i.e., about 760 mm. Hg and 22°C.

Following is an example of how the volumes of stored CO₂ were calculated. R. Q. of the initial time period = .86. R. Q. at the end of the period of inhalation of CO₂ rich air = .65. The CO₂ production = 65 liters and the O₂ consumption = 100 liters. If the R. Q. had remained constant and there were 100 liters O₂ consumption, there would have been 86 liters of CO₂ production, e.g., $\frac{86}{100} = \text{R. Q. of .86}$. The CO₂ stored then = 86 - 65 = 21 liters.

The Effect of Inhalation of Air Initially High in CO₂
on the Respiratory Quotient

The R. Q.'s of men during inhalation of CO₂ rich air are shown in Table II. This work was done using air initially high in CO₂ rather than producing CO₂ rich air by allowing CO₂ to accumulate from expired air as in most other tests. This procedure was used to test for the significance of the duration of exposure and the changes in pO₂, both of which were kept at a minimum in this series. The R. Q.'s averaged .56 and only two were above the lowest theoretical R. Q. of .707.

The data of the R. Q.'s of mice exposed to rebreathing air initially rich in CO₂ presented in Table XIII are also presented in Figures 5 and 6. The data are repeated in Table XIII because the time periods between collection of samples varied with the initial percentage of CO₂. This difference in time could not be presented in Figures 5 and 6. Table XVI lists the CO₂ and O₂ content of the air inhaled by the mice and Table II lists the initial CO₂ percentages inhaled by men. Because of the effect of high CO₂ on humans, it was not possible to continue the runs longer than the time necessary for the collection of sufficient gases to obtain an analysis of the respiratory exchanges. The men voluntarily terminated most of the runs, sometimes soon after 10 minutes of rebreathing, thus only initial R. Q.'s are given. In Figure 13 is shown the relationship that existed between initial CO₂ percentages and R. Q.'s of mice. From the limited available data, there appeared to be a straight line relationship.

"Recovery" from Inhalation of CO₂ Rich Air

Tables III and IV show the response of humans and dogs to inhalation of CO₂ rich air followed by inhalation of atmospheric air during a

"recovery" period. These experiments were undertaken to test for the release of CO₂ stored in the body during inhalation of CO₂ rich air. Because several factors could have affected the storage and subsequent release of CO₂, data that might be pertinent to an interpretation of these processes are included in Tables III and IV. Additional data that might be useful in this respect are found in Table XII which gives the O₂ consumption and the CO₂ production of the dogs during the period of rebreathing, Table XI which gives the O₂ consumption and CO₂ production of humans during the period of rebreathing, and Tables XIX and XX which give the percent CO₂ and O₂ of the air inhaled by humans and dogs respectively. The length of time between samples in the recovery period for both man and dogs varied because of the limited volume of the Douglas bags in which the expired air was collected. The bags were often filled before the time originally set for changing to another bag for collection of a new sample.

Some humans and dogs, apparently by hyperventilation, blew off more CO₂ during the "recovery" than the calculations showed was stored during inhalation of CO₂ rich air. These extra quantities are listed under the column headed "Liters of CO₂ released in addition to that stored".

In another study of the "recovery" from breathing air high in CO₂, humans were used (Group "H") and alveolar samples were collected during the recovery period. These data are presented in Figure 21. The rise in the R. Q.'s above unity at the 15 second, 45 second, and two minute samples is obvious for no determination was below an R. Q. of 1; and in the 45 second alveolar samples, the lowest value recorded was 1.47 and the highest, 2.37. From four minutes to 15 minutes, as indicated by the plateau on the Figure, the R. Q.'s were approximately .90 with few determinations above unity. As the means were much lower, these three values recorded above unity were ascribed to chance or error.

Temperature Drop of Rats and Mice

One response of rats and mice to the stress of the experiments was a drop in body temperature. The initial and terminal temperatures and temperature drop of mice and rats are shown in Table V. The values are reported as collected, i.e., degrees in Fahrenheit for mice and centigrade for rats. The mean of the Fahrenheit temperatures for mice is converted into centigrade units for comparison with the data collected for rats. Since the highest values of the terminal temperatures are, in every case, lower than the lowest values of the initial temperatures, there is obviously a significant drop in the body temperature of the mice and rats. The "t" test for the difference between the initial and terminal temperature of mice is 13.44, a highly significant difference, and that for the difference between the initial and terminal temperature of rats is 6.86, also a highly significant difference.

Respiratory Quotients of Mice, Rats, and Humans During Rebreathing of Air in Which Expired CO₂ was Allowed to Accumulate

Respiratory Quotient of Mice. — In Figure 1 are shown the R. Q.'s of mice rebreathing in a chamber of 2,775 ml. volume in which CO₂ was allowed to accumulate. The individual determinations are shown and the means are connected by a graph line. Two or more identical determinations are listed beside each other horizontally. The drop in the R. Q. is somewhat masked in Figure 1 because the high values for the R. Q.'s at the beginning of the run accumulatively affected the values in the latter part of the run. In Figure 2 are presented the R. Q.'s for the individual time periods, e.g., the R. Q.'s for the period between 30 and 40 minutes. These are called "period" R. Q.'s. A statistical analysis of the data in Figure 1 shows that the difference between the 20 minute and the

120 minute observation is a "T" of 8.42. Similar analysis for Figure 2 produced a "T" of 8.41; for Figure 3, between 10 minute and 60 minute analysis, a "T" of 3.70; and for Figure 4 between the 10 minute and 60 minute analysis again a "T" of 3.88. All the above "T" values indicate highly significant differences. Figures 3 and 4 present data for mice rebreathing in a chamber of 955 ml. volume and Figures 1 and 2 are for mice rebreathing in a volume of 2,775 ml. Two chamber sizes were used to test for the influence of time.

In Figures 5 and 6 are shown the R. Q.'s of mice exposed to rebreathing a mixture of gases initially high in CO_2 . This was produced by the addition of CO_2 to normal atmospheric air. Expired CO_2 was allowed to accumulate. There was no significant change in the R. Q. over the course of the experiment as determined by the "T" test.

Respiratory Quotient of Rats. -- The "accumulative" R. Q.'s for rats rebreathing in a 2,775 ml. chamber in which CO_2 was allowed to accumulate are shown in Figure 7. The "period" R. Q.'s are presented in Figure 8. It is obvious from the shapes of the curves and the nature of the ranges of the determinations that in neither of the two graphs was there a statistical change from the beginning to the end of the experiment.

The "accumulative" and "period" R. Q.'s for rats rebreathing in a 7,100 ml. chamber in which expired CO_2 was allowed to accumulate are shown in Figures 9 and 10 respectively. The difference between the 20 minute and 100 minute analysis is a "T" of 2.32 or a non-significant difference (level between .1 and .05) in Figure 9 for "accumulative" R. Q.'s and a "T" of 1.83 or a non-significant difference (level between .1 and .2) in Figure 10 for "period" R. Q.'s. Statistics mean little here

because only 5 animals were used. Since this was one of several groups subjected to the same treatment, statistical validity was not necessary in all experiments.

Respiratory Quotient of Humans. -- In Figures 11 and 12 are shown the "accumulative" and "period" R. Q.'s for humans rebreathing volumes of 100 to 200 liters. Expired CO_2 was allowed to accumulate. A "T" test for the R. Q. drop in Figure 11 yielded a value of 4.50 and in Figure 12 a similar test gave a "T" value of 6.66, both highly significant.

The values for "period" R. Q.'s were obtained by successive subtraction of the figures from which the "accumulative" R. Q.'s were calculated. Air samples were drawn periodically and analyzed. From the data thus collected, the total gaseous exchange to the time of sampling was calculated. The R. Q.'s and the oxygen consumptions for individual time periods were calculated by subtracting the values for the beginning of the period from the values for the end of the period, e.g., the 30 minutes figures from the 40 minutes figures. The values for the "period" R. Q.'s vary more from the mean than do the values for "accumulative" R. Q.'s. This is because the accuracy of the Haldane-Henderson gas analysis apparatus is not sufficient to yield figures in all analyses, which when subtracted, as above indicated, produce precise R. Q.'s for the individual periods. The consistent fall in the "accumulative" R. Q.'s, however, indicates progressively lower "period" R. Q.'s which is substantiated by curves for the "period" R. Q.'s. This explanation holds for the relationship of Figures 1 and 2, 3 and 4, 5 and 6, 7 and 8, 9 and 10, 11 and 12.

Oxygen Consumption as Affected by Inhalation of CO_2 Rich Air

In Figures 14 to 21 inclusive, the O_2 consumptions are presented on a percentage basis. That is, they are shown as percentages of the O_2 consumption of the initial time period. The O_2 consumption of the first time period studied was taken as 100% and subsequent rates are expressed as percentages of this initial period. The reasons for this method of presentation are presented under the discussion section of this paper. The raw data expressed in ml. at ambient conditions is shown in Tables III, IV, VI, VII, VIII, IX, X, XI, and XII. The statistical analysis below was done using raw data, i.e., the volumes in ml.

Oxygen Consumption of Mice. -- As shown in Figure 14, there is a highly significant difference between the initial O_2 consumption and that measured between 100 and 120 minutes. The value for the "T" test was 7.74. It is noted that the slope of the curve changed at 80-100 minutes. In the last part of the run, the animals seemed to respond in two divergent manners: the one group maintaining a fall in O_2 consumption and the other group establishing a steady state. Because of the small number of samples in each group, it was impossible to make a statistical treatment of these apparently divergent results. A comparison of the scale of the abscissa in Figures 14 and 15 shows the time to be twice as long in Figure 14 as in Figure 15. The slopes of the curves, as drawn, on the first part of the graphs are similar but when the time is taken into consideration, it is evident that the slope of the curve in Figure 15 is twice that of Figure 14, i.e., the O_2 consumption of the mice in Group "B" in the smaller chamber dropped twice as fast as that of the mice in the larger chamber. The O_2 consumption of the mice in Group "B" (Figure 15) dropped more than 50% during the one hour run. The "T" value was 9.41, a highly significant level.

Figure 16 indicates the drop in O_2 consumption of mice exposed to rebreathing an atmosphere initially high in CO_2 . The "T" value for the difference between the O_2 consumption of the first and fourth time periods is 3.10 a significant level. The time periods for individual animals, as indicated in Table VIII, was intentionally varied with the initial CO_2 percentage, so as to keep as nearly uniform as possible the number of time periods in a test regardless of the initial percent CO_2 .

Oxygen Consumption of Rats. -- The O_2 consumption of rats as affected by inhalation of CO_2 rich air is shown in Figures 17 and 18. Figure 17 is the presentation of the O_2 consumption of rats in a chamber of 2,778 ml. The drop is highly significant with a "T" value of 5.93. In Figure 18 are presented the O_2 consumptions of rats in the larger chamber, 7,100 ml. Again the drop is highly significant with a "T" value of 4.62. A comparison of the slopes of the cruves over the first part of the run shows the drop to be more than four times as fast in the smaller chamber (Figure 17, Group "B").

Oxygen Consumption of Humans. -- There was no statistically significant change in the O_2 consumption of humans as a result of rebreathing air in which CO_2 was allowed to accumulate.

Oxygen Consumption During "Recovery" While Breathing Atmospheric Air After Inhalation of CO_2 Rich Air

The O_2 consumptions of men and dogs during rebreathing of air in which CO_2 was allowed to accumulate and during the recovery which followed while breathing atmospheric air are shown in Figures 19 and 20. It is noted that during the first few minutes of recovery, there was an increase in the O_2 consumption which in humans was eleven-fold more than the normal O_2 consumption. In dogs, over the first three minutes of recovery, the increase was nearly three-fold.

CO₂ Increase with Time

Most R. Q.'s and O₂ consumption responses of the experimental animals are plotted against time in the above tables and figures. They could have been plotted against per cent CO₂. The increase in percent CO₂ in the inspired air is plotted against time in Figure 22. This makes possible a comparison of the percent CO₂ with the responses.

TABLE I

CO₂ Stored in the Bodies of Mice, Rats, Dogs, and Monkeys Induced by CO₂ with Air
(Volume in ml. at Ambient Conditions)

Mice			Rats			Dogs			Monkeys		
1 hr.	2 hr.	3 hr.	1 hr.	2 hr.	3 hr.	1 hr.	2 hr.	3 hr.	1 hr.	2 hr.	3 hr.
Run	Run	Run	Run	Run	Run	Run	Run	Run	Run	Run	Run
Group B	Group A	Group A	Group B	Group B	Group B	Group B	Group B	Group B	Group B	Group B	Group B
Anti- mal. wt. (gr.)	Anti- mal. wt. (gr.)	Anti- mal. wt. (gr.)	Anti- mal. wt. (gr.)	Anti- mal. wt. (gr.)	Anti- mal. wt. (gr.)	Anti- mal. wt. (gr.)	Anti- mal. wt. (gr.)	Anti- mal. wt. (gr.)	Anti- mal. wt. (gr.)	Anti- mal. wt. (gr.)	Anti- mal. wt. (gr.)
CO ₂ stored	CO ₂ stored	CO ₂ stored	CO ₂ stored	CO ₂ stored	CO ₂ stored	CO ₂ stored	CO ₂ stored	CO ₂ stored	CO ₂ stored	CO ₂ stored	CO ₂ stored
22.5	11	36.7	33	355	315	42	1,030	50	1,681	50	1,681
23.0	6	24.1	50	300	390	66	860	70	1,619	70	1,619
27.0	10	24.8	37	280	423	105	1,010	60	1,301	60	1,301
24.9	16	27.1	19	267	450	130	860	50	2,510	50	2,510
27.4	22	30.2	45	390	455	24	700	50	2,110	50	2,110
31.0	8	25.1	51	375	455	24	600	40	1,001	40	1,001
32.5	6	24.9	50	363	455	24	600	32	1,413	32	1,413
32.0	27	22.0	19					50	830	50	830
35.4	24	22.9	22					50	1,160	50	1,160
Av.	14	23.4	21					39	250	39	250
		Av.	35					65	3,840	65	3,840

TABLE II

R. Q. of Men Inhaling Air Initially
Rich in CO₂ -- Group I

Initial CO ₂ percent	5.70	7.38	8.62	5.42	2.83	6.11	6.77	9.49
R. Q. of First 10 Min. Period	.36	.59	.49	.62	.74	.50	.77	.45

Average R. Q. = .56

TABLE III

CO₂ Exchange and R. Q.'s of Humans During Inhalation of CO₂
 Rich Air and During Recovery While Inhaling Atmospheric Air --- Group G

Sub- ject	Dura- tion of ex- posure (min.)	Liters of CO ₂ stored	Liters of CO ₂ Re- covered	Liters of CO ₂ not Re- covered	Liters in ad- dition to that stored	R. Q.'s During Exposure** (minutes)										R. Q.'s During Recovery Time periods (in minutes) as indicated in the upper figures of each row					
						10	20	30	40	50	60	70	74	77	79	81	83	85	87	89	91
						10	20	30	40	50	60	70	74	77	79	81	83	85	87	89	91
1 st	65	14	1.73	.74	.99	98	88	82	78	77	77	74	74	77	79	81	83	85	87	89	91
2 nd	39	9	1.17	1.43	.26	77	77	76	75	75	77	77	74	77	79	81	83	85	87	89	91
3 rd	50	8	1.04	.06	.98	88	81	81	81	81	81	81	81	81	81	81	81	81	81	81	81
4 th	50	11	.83	.59	.24	78	81	81	81	81	81	81	81	81	81	81	81	81	81	81	81
5 th	32	7	1.41	2.00	.59	92	89	80	79	79	79	79	79	79	79	79	79	79	79	79	79
6 th	50	10	1.68	.57	1.12	92	91	86	83	82	82	82	82	82	82	82	82	82	82	82	82

** Upper figures in each row are total R. Q.'s to time of sample; lower figures in each row are R. Q.'s of previous 10 minute period.

* CO₂ exchanges based on R. Q. of .85. This was done because the initial R. Q. was low.

7 CO₂ exchanges based on R. Q. of .81.

8 CO₂ exchanges based on initial R. Q. of exposure period.

All volumes at ambient conditions of temperature and pressure.

TABLE IV

CO₂ Exchange and R. Q.'s of Dogs During Inhalation of CO₂
 Rich Air and During Recovery While Inhaling Atmospheric Air -- Group J

Dog No.	Duration of exposure (min.)	Liters of ex-posed CO ₂ covered	Liters of CO ₂ not covered	Liters of CO ₂ in addition to that stored covered	R. Q.'s During Exposure** (minutes)						R. Q.'s During Recovery Time periods (in Minutes) as indicated in the upper figures of each row			
					10	20	30	40	50	60				
					76	69	63				3	7	10	14
53	30	44	1.08	.52	.56	76	64	54			.95	.94	.93	.86
58	30	20	.86	.53	.33	73	69	67			3	7	10	
						73	67	62			.87	1.01	.74	
42	50	50	1.01	.63	.38	70	67	68	68	68	3	7	10	20
						70	64	71	67	70	.99	.95	.94	.96
43	60	60	.86	2.21		80	66	66	60	67	3	7	10	20
					1.35	80	54	66	65	70	1.23	1.33	1.01	1.07
														2.30
44	50	40	.70	.73	.03	79	69	69	69	69	3	7	10	20
						79	60	70	70	70	1.06	1.07	.99	.97
60	30	40	.60	2.11	1.50	72	72	71			3	8	9	11
						72	73	68			1.11	1.20	1.35	.93
														1.00

** Lower figure in each row is total R. Q. to time of sample; lower figure in each row is R. Q. of previous ten minute period.

All volumes at ambient conditions of temperature and pressure.

TABLE V

Temperature Drop of Mice and Rats Exposed to
Rebreathing Air in Which the Expired CO₂
Was Allowed to Accumulate

Mice Group B			Rats Group D		
Temperature in °F			Temperature in °C		
Initial	Terminal	Temp. Drop	Initial	Terminal	Temp. Drop
98.2	90.3	7.9	35.0	33.5	1.5
97.4	91.5	6.9	35.5	31.3	4.2
97.9	89.1	8.8	36.5	30.1	6.4
98.5	88.4	10.1	35.2	26.5	8.7
87.8	90.3	7.5	36.2	31.2	5.0
99.0	93.3	5.7	35.9	32.0	3.9
99.5	92.3	7.2	36.8	32.0	4.8
100.1	89.6	10.5	34.9	31.9	3.0
98.3	92.4	5.9	35.7	29.8	5.9
97.5	90.3	7.2	36.4	33.4	3.0
$\bar{x} = 7.80^{\circ}\text{F}$ or 4.30°C			$\bar{x} = 4.6$		

S. D. initial temp. = .833
S. D. terminal temp. = 1.495
t = 13.44 highly significant

S. D. initial temp. = .209
S. D. terminal temp. = .6429
t = 6.86 highly significant

TABLE VI

Oxygen Consumption and Carbon Dioxide Production of Mice
Rebreathing Air in Which Expired CO₂ was Allowed to Accumulate --- Group A

Time in Minutes	Animal Weight (grams)									
	36.7	24.1	24.8	27.1	30.6	25.1	24.9	22.9	22.9	23.4
20	65.00	52.50	56.60	52.85	64.90	45.79	51.59	45.15	42.43	41.30
	65.35	52.50	60.11	64.05	69.46	48.60	55.51	53.21	47.00	47.27
40	41.43	44.37	40.15	44.92	42.08	38.94	40.38	22.35	29.79	31.71
	58.83	55.44	56.40	53.61	55.28	53.19	50.46	25.82	39.44	38.64
60	45.45	39.89	38.10	29.71	42.64	38.39	28.38	24.55	25.61	25.23
	53.98	43.70	46.67	48.44	56.58	49.33	36.93	38.97	31.01	37.55
80	33.12	16.99	29.54	32.06	32.67	28.26	26.02	16.02	18.50	26.37
	42.21	34.74	41.25	38.31	49.70	45.08	40.57	22.41	30.38	27.17
100		25.17	29.24	25.55	25.47	24.85	31.38	17.01	21.85	18.21
		28.17	34.19	35.42	30.28	35.71	50.99	26.69	25.46	24.22
120		28.61	20.98	18.56	19.97	24.42	22.01	15.89	20.30	17.02
		43.54	38.08	28.94	30.94	35.76	36.22	21.76	26.94	34.58

Each figure represents exchange for the former 20 minute period.

Volumes expressed in ml. at ambient conditions of temperature and pressure.

Upper row of figures is CO₂ production.

Lower row of figures is O₂ consumption.

TABLE VII

Oxygen Consumption and Carbon Dioxide Production
of Mice Rebreathing Air in Which Expired CO_2
Was Allowed to Accumulate -- Group B

Time (in min.)	Animal Weight (grams)									
	22.5	23.0	27.0	24.9	27.4	31	32.5	32	35.4	
10	24.23	18.62	27.97	22.67	24.35	26	25	26	23	
	24.92	23.26	31.58	25.01	24.35	35	31	23	24	
20	16.47	18.62	21.17	15.32	18.88	18	21	25.5	19	
	21.21	23.26	24.80	17.62	22.10	22	28	28	26	
30	13.58	13.00	16.74	10.25	18.84	13	17	17	18	
	20.77	18.53	18.87	18.24	22.79	21	23	24	23	
40	10.61	9.21	12.68	12.73	13.36	12	12	12	12	
	15.72	13.10	22.23	17.91	17.98	15	17	20	19	
50	10.61	10.02	10.53	10.59	12.71	8	11	8	9	
	25.72	12.15	13.09	14.39	15.61	14	16	13	12	
60	8.27	6.19	7.89	8.98	8.26	7	8	6	6	
	11.50	11.19	9.86	12.99	15.80	12	9	8	12	

Each figure represents exchanges for the previous 10 minute period.
Volumes expressed in ml. at ambient conditions.
Upper figures in each row are CO_2 production.
Lower figures in each row are O_2 consumption.

TABLE VIII

O₂ Consumption and CO₂ Production of Mice Exposed to
Rebreathing an Atmosphere Initially High in CO₂ -- Group C

Time Period	Animal Weight											
	44.0	43.6	47.1	39.2	44.5	40.8	45.0	43.5	36.9	44.8		
	Time in Minutes											
	20	10	17	15	20	16	15	15	15	15		
1	35.98 54.68	11.54 22.35	33.76 51.11	34.54 47.69	63.83 77.5	30.59 44.67	32.57 42.05	37.30 59.80	13.40 32.22	17.48 35.73		
2	33.57 43.77	16.76 25.23	33.67 50.32	33.11 43.16	49.97 60.65	22.24 52.73	26.32 36.04	37.61 53.11		15.35 25.63		
3	28.59 46.23	17.29 20.85	32.06 47.31	25.85 44.62	36.40 51.94	12.3 11.3	19.20 30.46	30.38 51.06				
4	26.81 38.15	11.26 18.82	33.15 39.67	21.28 34.42	35.92 48.54	12.9 27.5	18.72 26.73	27.86 38.47				
5		16.15 28.86		20.07 30.23			25.02 31.90	17.04 30.16				
6		14.07 14.99		16.27 34.42								

Figures represent exchanges for the previous time period.

Time periods indicated for each animal vary with initial percent CO₂.

Volumes expressed in ml. at ambient conditions.

Upper figures in each row are CO₂ production.

Lower figures in each row are O₂ consumption.

TABLE IX

O_2 Consumption and CO_2 Production of Rats Rebreathing
Air in Which Expired CO_2 was Allowed to Accumulate -- Group D

Time in Minutes	Animal Weight (grams)						
	355	300	280	267	390	275	323
10	116	98	55	89	113	96	83
	134	136	83	123	148	125	88
20	74	50	32	68	70	71	55
	98	73	42	86	90	87	82
30	46	41	35	52	57	65	60
	65	57	54	65	80	84	65
40	41	44	37	30	35		29
	68	66	54	51	45		37
50		32	38				
		30	53				
60			25				
			38				

Each figure represents exchange for previous ten minute period.

Volumes expressed in ml. at ambient conditions of temperature and pressure.

Upper figure in each row is CO_2 production.

Lower figure in each row is O_2 consumption.

TABLE X

O₂ Consumption and CO₂ Production of Rats Rebreathing air in Which
Expired CO₂ was Allowed to Accumulate -- Group B

Time in Minutes	Animal Weight (grams)				
	315	390	423	450	455
20	158	178	269	245	185
	184	203	284	257	233
40	147	120	155	179	181
	184	141	197	241	222
60	159	127	172	141	146
	166	150	189	166	182
80	81	113	115	123	100
	111	130	165	154	155
100	39	92	80	119	96
	76	154	115	157	123
120	22	86			
	32	121			

Each figure represents exchanges for the previous
ten minute period.

Volumes expressed in ml. at ambient conditions.

Upper figures in each row are CO₂ production.

Lower figures in each row are O₂ consumption.

TABLE XI

O₂ Consumption and CO₂ Production of Humans Rebreathing Air in Which
Expired CO₂ was Allowed to Accumulate -- Group F

Time in Minutes	Subjects									
	1	2	3	4	5	6	7	8	9	10
10	3.05	2.41	4.53	3.73	4.12	3.16	3.70	1.72	1.89	2.24
	3.32	2.90	5.26	3.95	4.61	3.62	4.04	2.20	2.14	2.91
20	2.47	2.01	2.32	2.49	2.46	2.62	2.54	2.15	1.75	2.29
	2.75	2.20	2.82	3.29	3.44	3.16	3.22	2.41	2.37	2.98
30	2.30	1.90	1.88	2.06	2.24	2.38	2.18	2.19	2.34	
	3.02	2.72	2.44	2.47	2.95	3.14	3.24	2.69	2.88	2.98
40	2.57	1.96	1.82	1.99	2.85	2.25	1.30	2.10	2.66	
	3.49	2.44	2.35	2.81	3.61	3.22	2.43	2.91	3.32	3.01
50	2.64	2.13	2.24	2.47	1.70			1.90	2.30	
	3.42	2.86	3.08	3.65	2.77			3.03	3.38	
60		2.06	2.30							
		2.35	3.11							
70		1.93								
		3.38								

Each figure represents exchange for the previous 10 minute period.

Volumes in liters at ambient conditions.

Upper figure in each row is CO₂ production.

Lower figure in each row is O₂ consumption.

TABLE XII

O₂ Consumption and CO₂ Production of Dogs Exposed to Rebreathing Air in Which the Expired CO₂ was Allowed to Accumulate -- Group J

Time in Minutes	Dog Number					
	53	58	42	43	41	60
10	.98	1.03	.93	.65	.67	.96
	1.29	1.41	1.33	.81	.85	1.34
20	1.00	1.30	.75	.55	.56	.96
	1.57	1.95	1.18	1.01	.94	1.32
30	1.08	.91	.80	.61	.64	1.06
	2.01	1.46	1.13	.91	.92	1.55
40			.77	.61	.65	
			1.15	.94	.97	
50			.84	.65	.61	
			1.21	.93	.27	
60				.53		
				.64		

Figures represent changes for the previous ten minute period.

Volumes expressed in liters at ambient conditions.

Upper figures in each row are CO₂ production.

Lower figures in each row are O₂ consumption.

TABLE XIII

R. Q.'s of Mice Exposed to Rebreathing Air Initially High in CO₂ --- Group C

Time Period	Duration in Minutes of the time periods											
	20	15	15	15	15	17	20	16	10	16	15	15
1	Initial % O ₂											
	Initial % CO ₂											
	Animal Weight (grams)											
2	Duration in Minutes of the time periods											
	Initial % O ₂											
	Initial % CO ₂											
3	Duration in Minutes of the time periods											
	Initial % O ₂											
	Initial % CO ₂											
4	Duration in Minutes of the time periods											
	Initial % O ₂											
	Initial % CO ₂											
5	Duration in Minutes of the time periods											
	Initial % O ₂											
	Initial % CO ₂											
6	Duration in Minutes of the time periods											
	Initial % O ₂											
	Initial % CO ₂											

Time periods vary with initial percent of CO₂.

The upper figure in each row is the total R. Q. to time of sampling.

The lower figure in each row is the R. Q. for previous time period.

TABLE XIV

The Percentages of CO₂ and O₂ of the Air Inhaled by Mice Rebreathing
in a 2.778 ml. chamber --- Group A

Time in Minutes	Animal Weight									
	16.7	24.1	24.8	27.1	30.2	25.1	24.9	22.0	22.9	23.4
20	2.34	1.89	2.04	1.91	2.34	1.65	1.86	1.63	1.53	1.49
	18.65	19.11	18.86	18.77	18.53	19.27	19.02	19.14	19.34	19.34
40	3.87	3.52	3.52	3.56	3.89	3.08	3.34	2.45	2.62	2.65
	16.64	17.02	16.92	16.87	16.60	17.43	17.25	18.25	17.97	17.98
60	5.56	4.99	4.94	4.69	5.51	4.51	4.40	3.37	3.57	3.63
	14.68	15.60	15.24	15.19	14.57	15.68	15.94	16.11	16.86	16.67
80	6.82	5.66	6.07	5.91	6.78	5.60	5.40	3.98	4.28	4.26
	13.15	14.42	13.76	13.80	12.79	14.09	14.51	16.11	15.80	15.66
100	6.62	7.19	7.19	6.90	7.77	6.57	6.63	4.69	5.11	5.32
	13.35	12.49	12.49	12.49	11.65	12.29	12.69	15.16	14.86	14.78
120	7.75	8.05	8.05	7.65	8.56	7.54	7.52	5.26	5.85	6.01
	11.77	11.11	11.11	11.42	10.50	11.47	11.35	14.36	13.76	13.56

Upper figures in each row are percentage CO₂.

Lower figures in each row are percentage O₂.

TABLE XV

The Percentage of CO₂ and O₂ of the Air Inhaled
by Mice Rebreathing in a 955 ml. chamber — Group B

Time (in min.)	Animal Weight									
	21	32.5	32	35.4	22.5	23.0	27.0	24.9	27.4	
10	2.87	2.81	2.83	2.54	2.55		2.94	2.36	2.55	
	17.33	17.67	18.78	18.36	18.06		17.76	18.43	18.45	
20	4.95	5.14	4.71	4.71	4.35	3.98	5.24	4.04	4.59	
	14.74	14.67	14.84	15.57	15.85	16.24	15.15	16.57	16.14	
30	6.55	7.28	7.71	6.77	5.91	5.42	7.14	5.22	6.69	
	12.54	12.06	12.15	13.00	13.66	14.27	12.80	14.69	13.70	
40	8.07	9.05	9.34	8.30		6.57	8.67	6.71	8.26	
	10.76	9.79	9.90	10.80		12.81	10.68	12.73	11.72	
50	9.13	10.47	10.37	9.45	8.61	7.78	9.97	8.00	9.79	
	9.08	7.89	8.34	9.43	10.04	11.39	9.14	11.08	9.92	
60	10.32	11.59	11.32	10.44	9.68	8.62	10.99	9.15	11.03	
	7.48	6.63	7.18	7.92	8.69	10.03	7.89	9.53	8.17	

Each figure represents exchanges for the previous ten minute period.
Upper figures in each row are percentages CO₂.
Lower figures in each row are percentages O₂.

TABLE XVI

The Percentages of CO₂ and O₂ of the Air Inspired by Mice Rebreathing
2778 ml. of Air Initially Rich in CO₂ -- Group C

Time Period	Duration in Minutes of the time periods														
	20	15	15	15	15	15	17	20	16	10	15	15	15	15	15
1	Initial % O ₂														
	19.24	19.10	18.74	18.52	18.70	17.00	17.64	18.05	17.98	17.87					
	4.39	5.45	5.68	6.26	6.77	6.79	7.48	8.03	11.21	12.07					
2	Initial % CO ₂														
	44.5	39.2	45.0	43.5	47.1	44.0	40.8	43.6	44.3	36.9					
	Animal Weight (grams)														
3	Duration in Minutes of the time periods														
	20	15	15	15	15	15	17	20	16	10	15	15	15	15	15
	6.72	6.73	6.88	7.69	8.04	8.15	8.63	8.46	11.92	12.64					
4	Initial % O ₂														
	16.64	17.46	17.28	16.49	16.96	15.12	16.11	17.31	16.80	16.76					
	Animal Weight (grams)														
5	Duration in Minutes of the time periods														
	20	15	15	15	15	15	17	20	16	10	15	15	15	15	15
	8.58	7.97	7.87	9.10	9.33	9.42	9.55	9.12	12.53						
6	Initial % CO ₂														
	14.43	15.94	16.02	14.64	15.21	13.56	14.35	16.44	15.92						
	Animal Weight (grams)														
7	Duration in Minutes of the time periods														
	20	15	15	15	15	15	17	20	16	10	15	15	15	15	15
	9.99	8.99	8.71	10.31	10.58	10.55	10.00	9.77							
8	Initial % O ₂														
	12.63	14.39	14.91	12.84	13.53	11.95	13.97	15.69							
	Animal Weight (grams)														
9	Duration in Minutes of the time periods														
	20	15	15	15	15	15	17	20	16	10	15	15	15	15	15
	11.39	9.84	9.44	11.41	11.81	11.62	10.54	10.22							
10	Initial % CO ₂														
	10.86	13.16	13.95	11.43	12.01	10.52	13.00	15.03							
	Animal Weight (grams)														
11	Duration in Minutes of the time periods														
	20	15	15	15	15	15	17	20	16	10	15	15	15	15	15
	10.65	10.41	12.13												
12	Initial % O ₂														
	12.05	12.78	10.32												
	Animal Weight (grams)														
13	Duration in Minutes of the time periods														
	20	15	15	15	15	15	17	20	16	10	15	15	15	15	15
	11.35														
14	Initial % CO ₂														
	10.87														
	Animal Weight (grams)														

Time periods vary with initial CO₂ percentages.
Upper figures in each row are percentage CO₂.
Lower figures in each row are percentage O₂.

TABLE XVII

The Percentages of CO_2 and O_2 of the Air Inhaled by Rats Rebreathing in a 2775 ml. chamber — Group D

Time in Minutes	355	300	280	267	390	275	323
	Animal Weight						
10	4.70	3.89	2.16	3.48	4.67	3.79	2.90
	15.74	15.91	17.88	16.44	15.21	16.32	17.63
20	7.78	5.58	3.46	6.24	7.63	6.64	5.19
	11.88	13.12	16.28	13.13	11.55	12.97	14.50
30	9.77	7.69	4.88	8.36	10.17	9.32	7.66
	9.24	10.81	14.31	10.56	8.22	9.67	11.82
40	11.65	9.64	6.43	9.68	11.75		8.92
	6.45	8.13	12.22	8.64	6.26		10.31
50		10.98	8.06				
		6.89	10.09				
60			9.18				
			8.51				

Upper figures in each row are percent CO_2
Lower figures in each row are percent O_2 .

TABLE XVIII

The Percentages of CO₂ and O₂ of the Air Inhaled by Rats
 Rebreathing in a 7100 ml. chamber — Group E

Time in Minutes	Animal Weight				
	315	390	423	450	455
10	2.33	2.63	3.96	3.61	2.74
	18.32	18.08	16.82	17.25	17.70
20	4.53	4.42	6.29	6.31	5.46
	15.73	15.99	14.01	13.83	14.50
30	6.90	6.31	8.89	8.43	7.67
	13.28	13.88	10.96	11.36	11.85
40	8.14	8.01	10.65	10.32	9.25
	11.69	11.98	8.84	9.10	9.61
50	8.82	9.46	11.92	12.07	10.74
	10.53	9.91	7.15	6.79	7.78
60	9.10	10.80			
	10.14	8.13			

Upper figures in each row are percent CO₂.
 Lower figures in each row are percent O₂.

TABLE XIX

The Percentages of CO₂ and O₂ of the Air Rebreathed by Humans ϕ - Group, F

Time in Minutes	Subjects										
	1	2	3	4	5	6	7	8	9	10	11
Liters Rebreathed	210.5	212.2	194	177.5	213	163.5	132.5	137.5	143	147	156
10	1.45 19.45	1.14 19.68	2.34 18.34	2.10 18.80	1.94 18.88	1.94 18.84	2.80 18.00	1.29 19.43	1.28 19.59	1.53 19.11	1.33 19.65
20	2.63 15.13	2.09 18.66	3.55 16.94	3.52 17.02	3.11 17.34	3.56 16.96	4.75 15.65	2.87 17.59	2.47 18.06	3.11 17.15	2.41 18.33
30	3.74 16.79	3.00 17.44	4.54 15.72	4.67 15.66	4.18 16.00	5.05 15.10	6.46 13.29	4.49 15.67	4.08 16.16	4.92 14.88	3.52 16.84
40	4.99 15.19	3.94 16.32	5.50 14.54	5.83 14.13	5.55 14.34	6.48 13.19	6.67 12.94	6.07 13.61	5.92 13.96	6.02 13.39	4.77 15.18
50	6.28 13.60	4.97 14.99	6.70 12.99	7.29 12.13	6.39 13.09			7.54 11.47	7.55 11.73		5.92 13.67
60		5.96 13.91	7.94 11.41								7.27 11.98

Upper figures in each row are percent CO₂.
 Lower figures in each row are percent O₂.

TABLE XX

The Percentages of CO₂ and O₂ of the Air Rebreathed
by Dogs in Group J

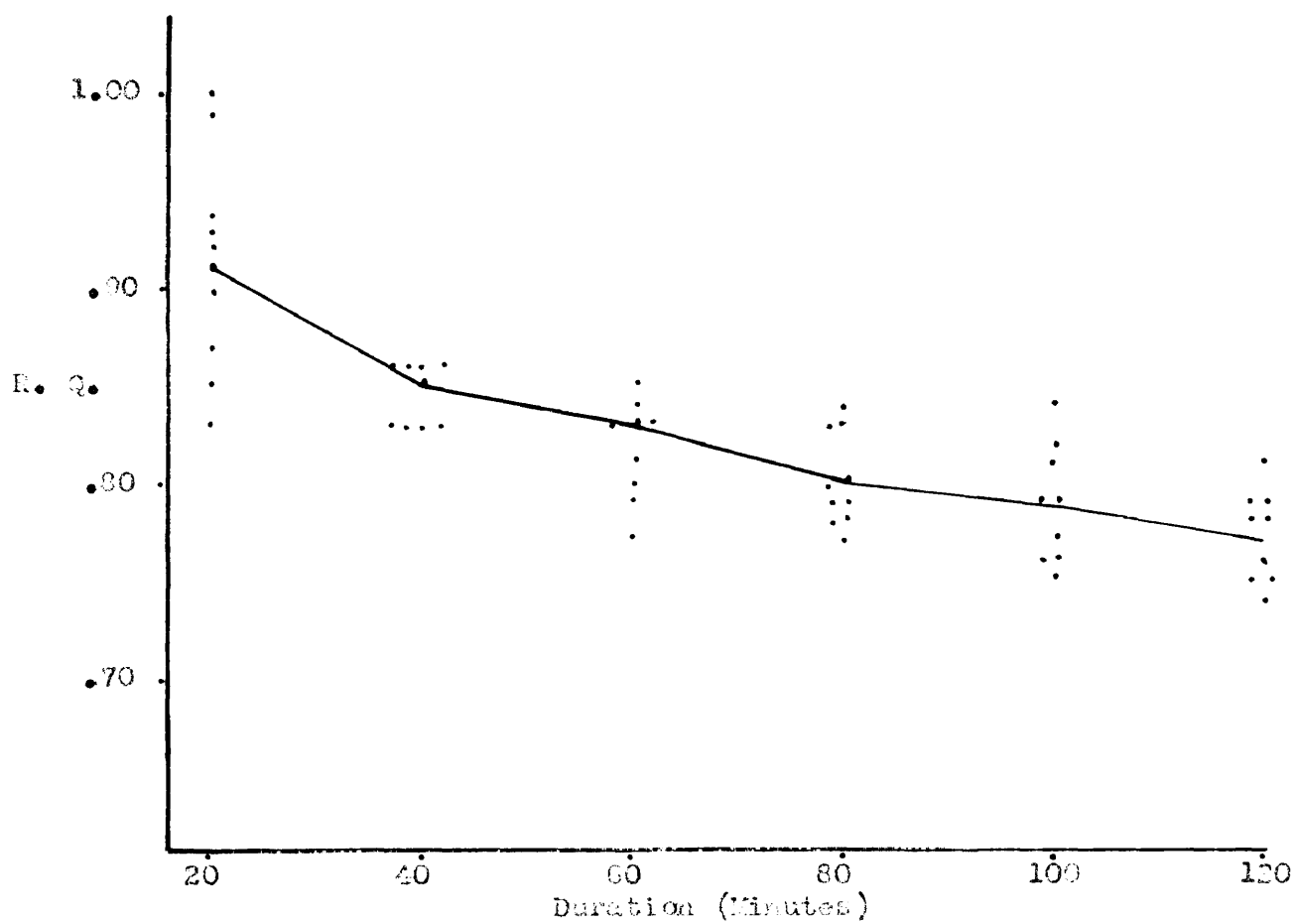
Time in Minutes	Subject					
	53	58	42	43	41	60
10	1.98	2.07	1.88	1.30	1.35	1.95
	18.53	18.32	18.49	19.45	19.36	18.47
20	4.05	5.24	3.42	2.50	2.59	4.24
	15.55	13.89	16.25	17.47	17.47	15.47
30	6.33	8.21	5.08	3.93	4.09	7.46
	11.86	9.71	14.05	15.49	15.44	11.08
40			6.71	5.49	5.78	
			11.78	13.27	13.17	
50			8.50	7.37	7.54	
			9.35	10.77	10.84	
60				9.38		
				8.72		

Upper figures in each row are percent CO₂.
Lower figures in each row are percent O₂.

Figure 1

Group A

The Accumulative Respiratory Quotients of Mice
Breathing in a Closed Chamber in Which
Expired CO_2 was Allowed to Accumulate

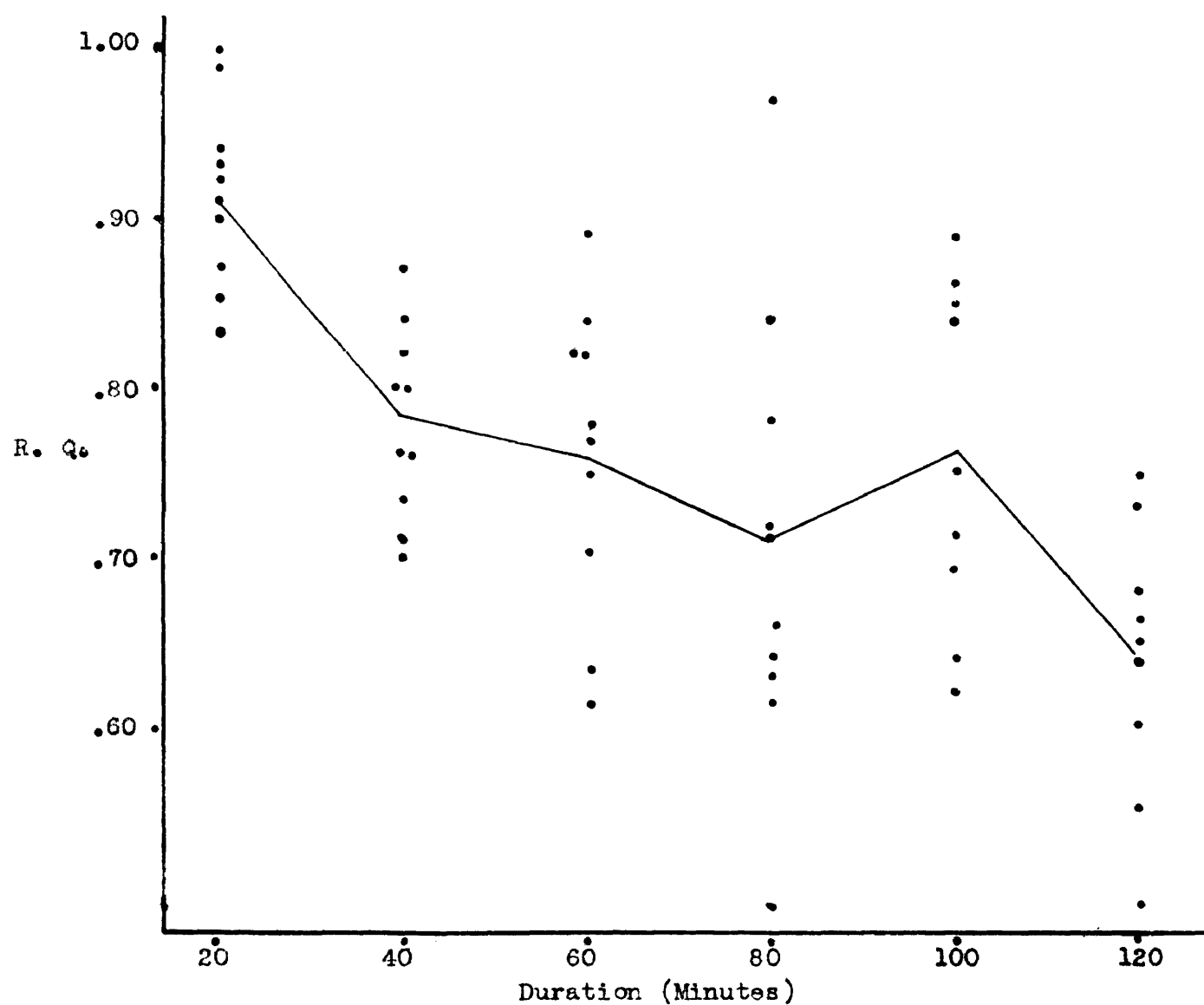


Dots represent individual determinations.

Figure 2

Group A

The Period Respiratory Quotients of Mice
Breathing in a Closed Chamber in Which
Expired CO_2 was Allowed to Accumulate

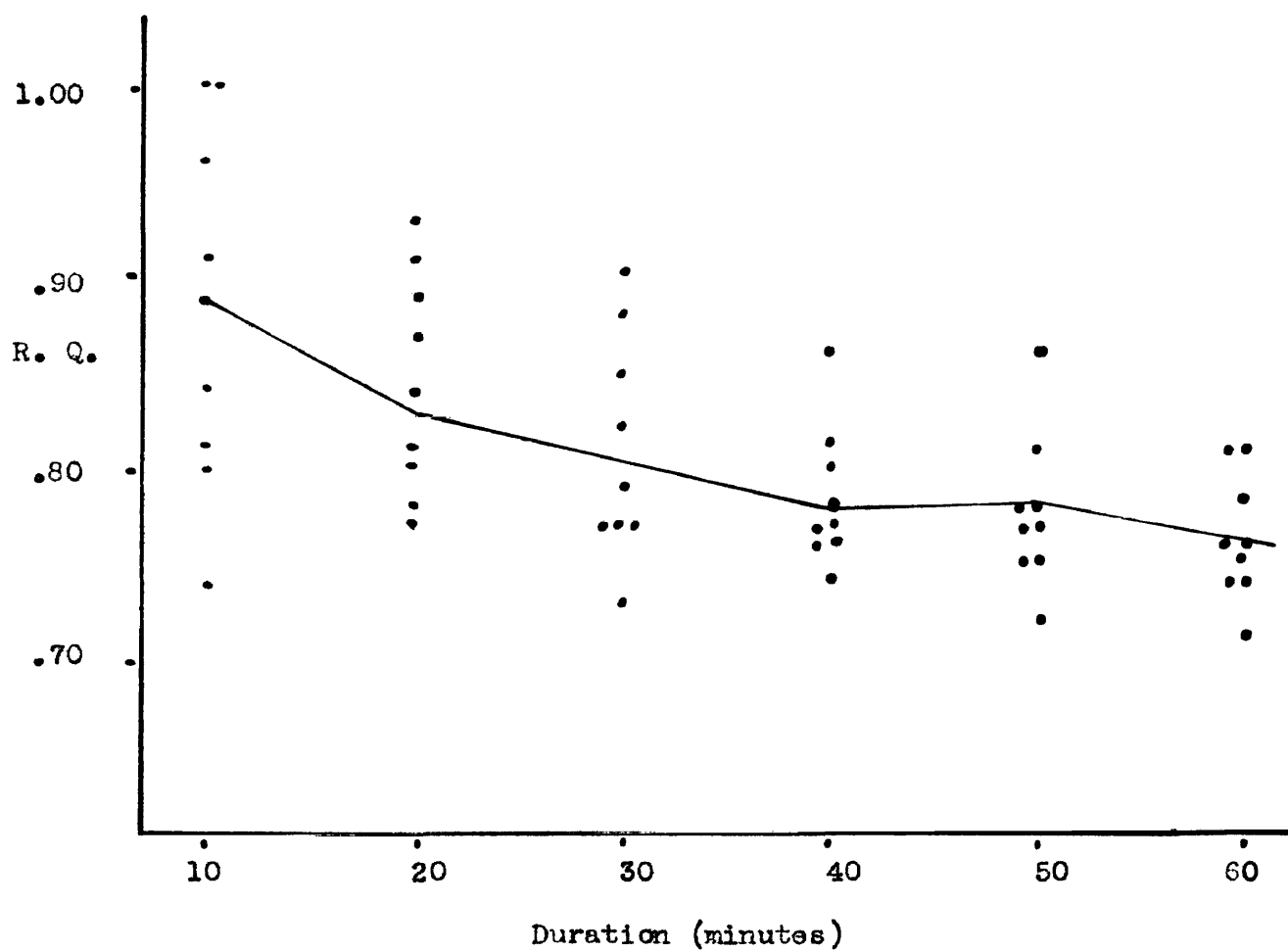


Dots represent individual determinations.

Figure 3

Group B

The Accumulative Respiratory Quotients of Mice Breathing
in a Closed Chamber in Which the Expired CO_2
was Allowed to Accumulate

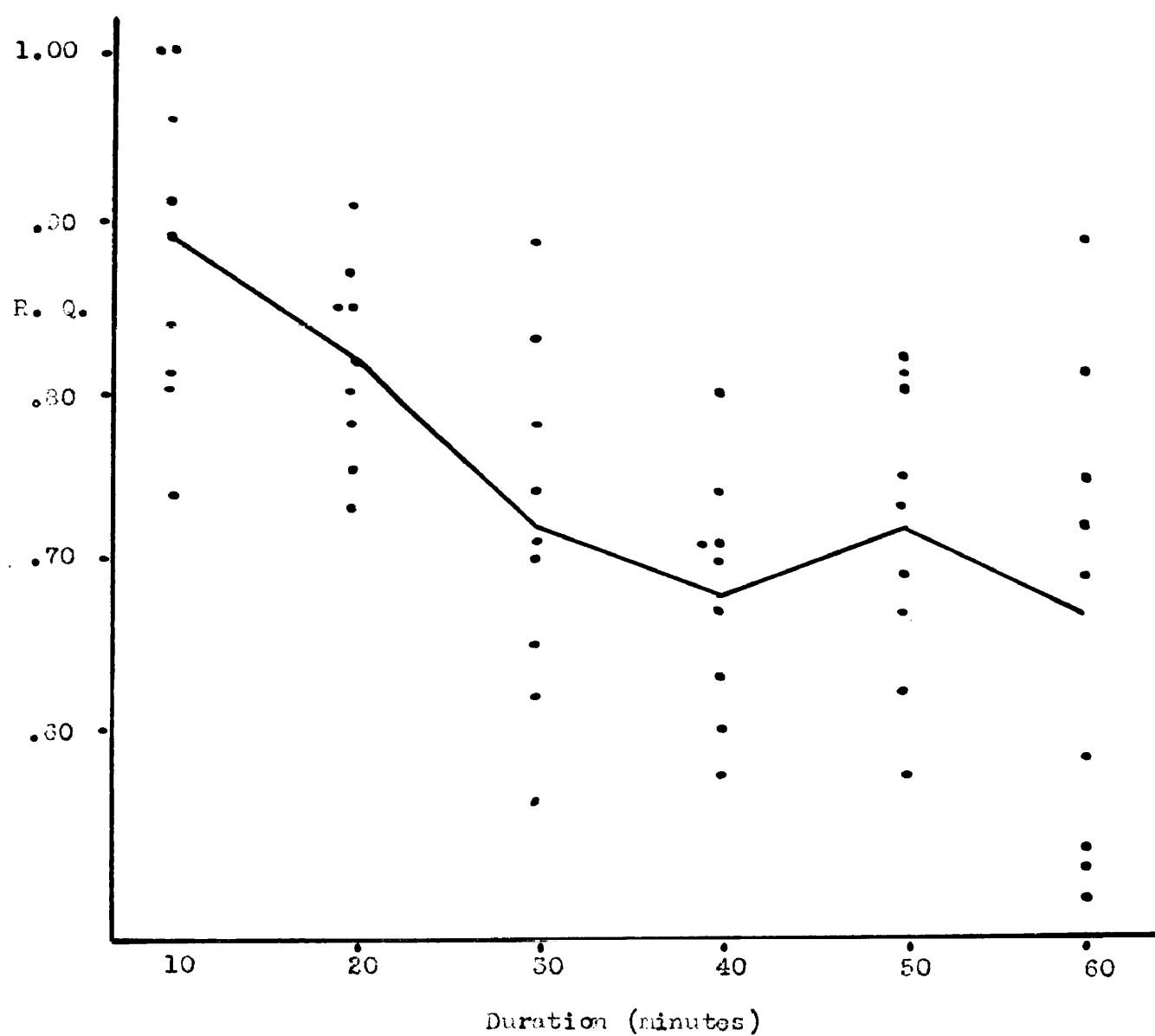


Dots represent individual determinations

Figure 4

Group B

The Period Respiratory Quotients of Mice Breathing
in a Closed Chamber in Which Expired CO_2 was
Allowed to Accumulate

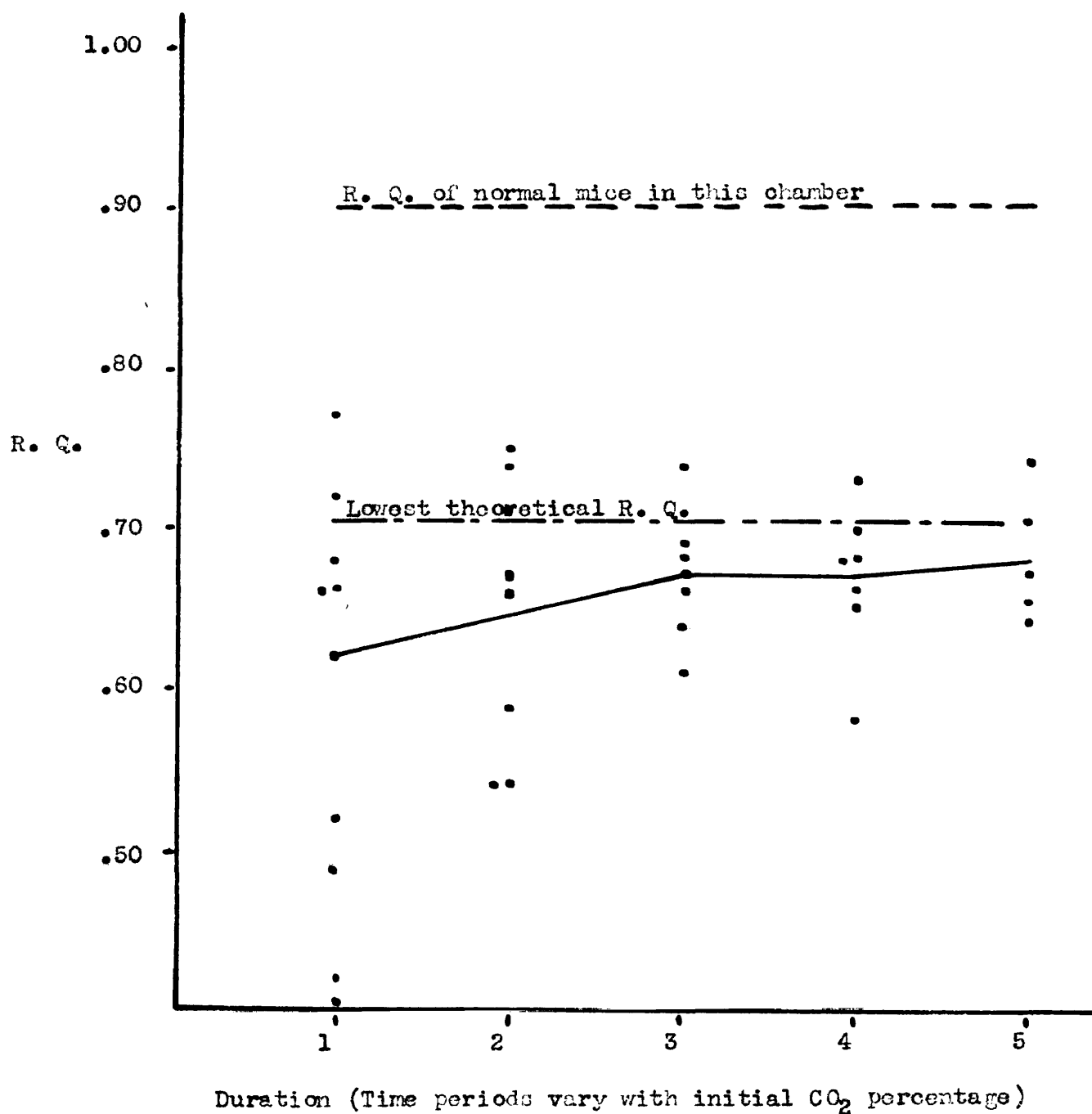


Dots represent individual determinations

Figure 5

Group C

The Accumulative Respiratory Quotients of Mice Breathing
in a Closed Chamber in Which Expired CO_2 was
Allowed to Accumulate. CO_2 Initially High

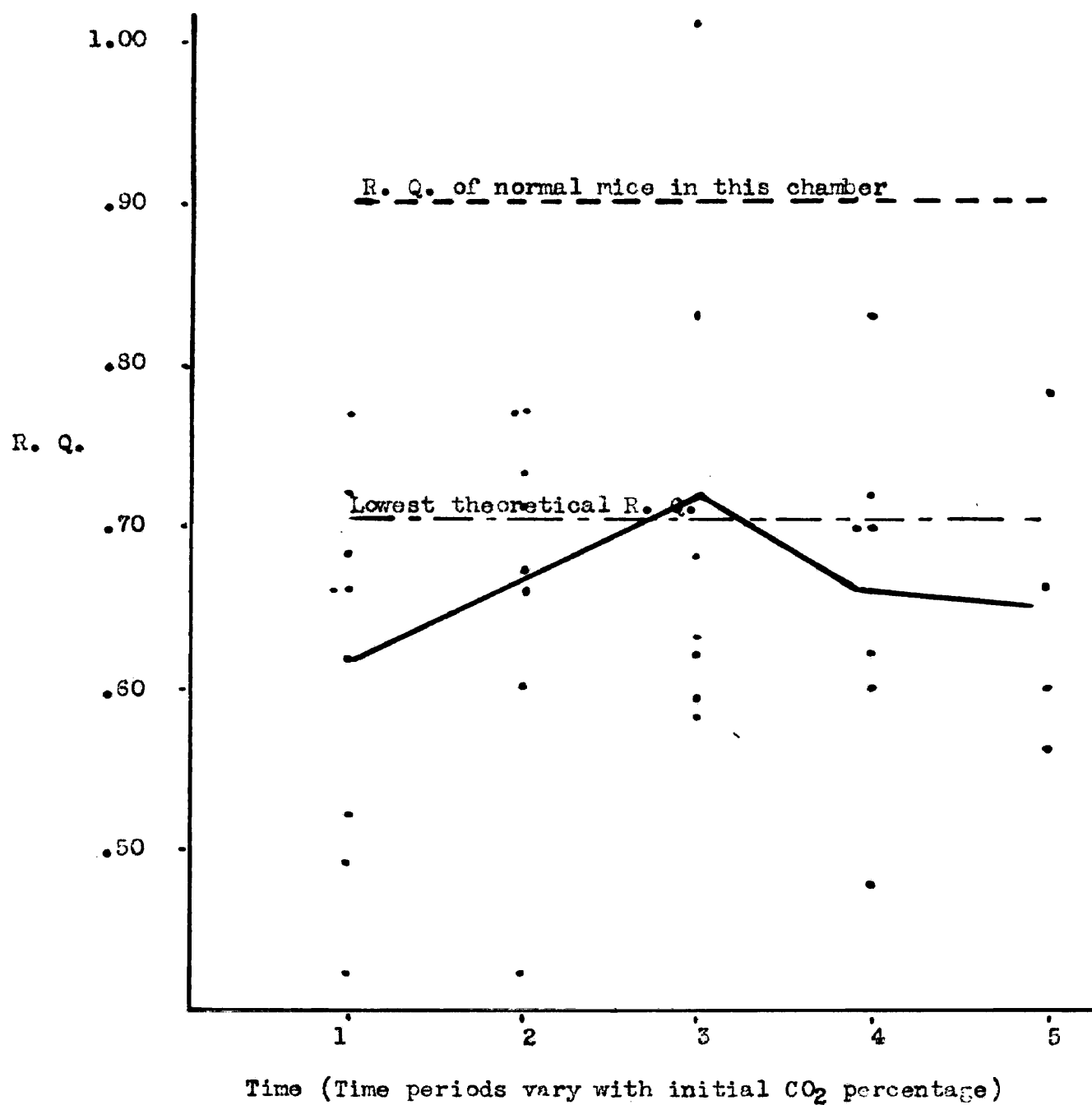


Dots represent individual determinations

Figure 6

Group C

The Period Respiratory Quotients of Mice Breathing
in a Closed Chamber in Which Expired CO_2 was Allowed
to Accumulate. CO_2 Initially High

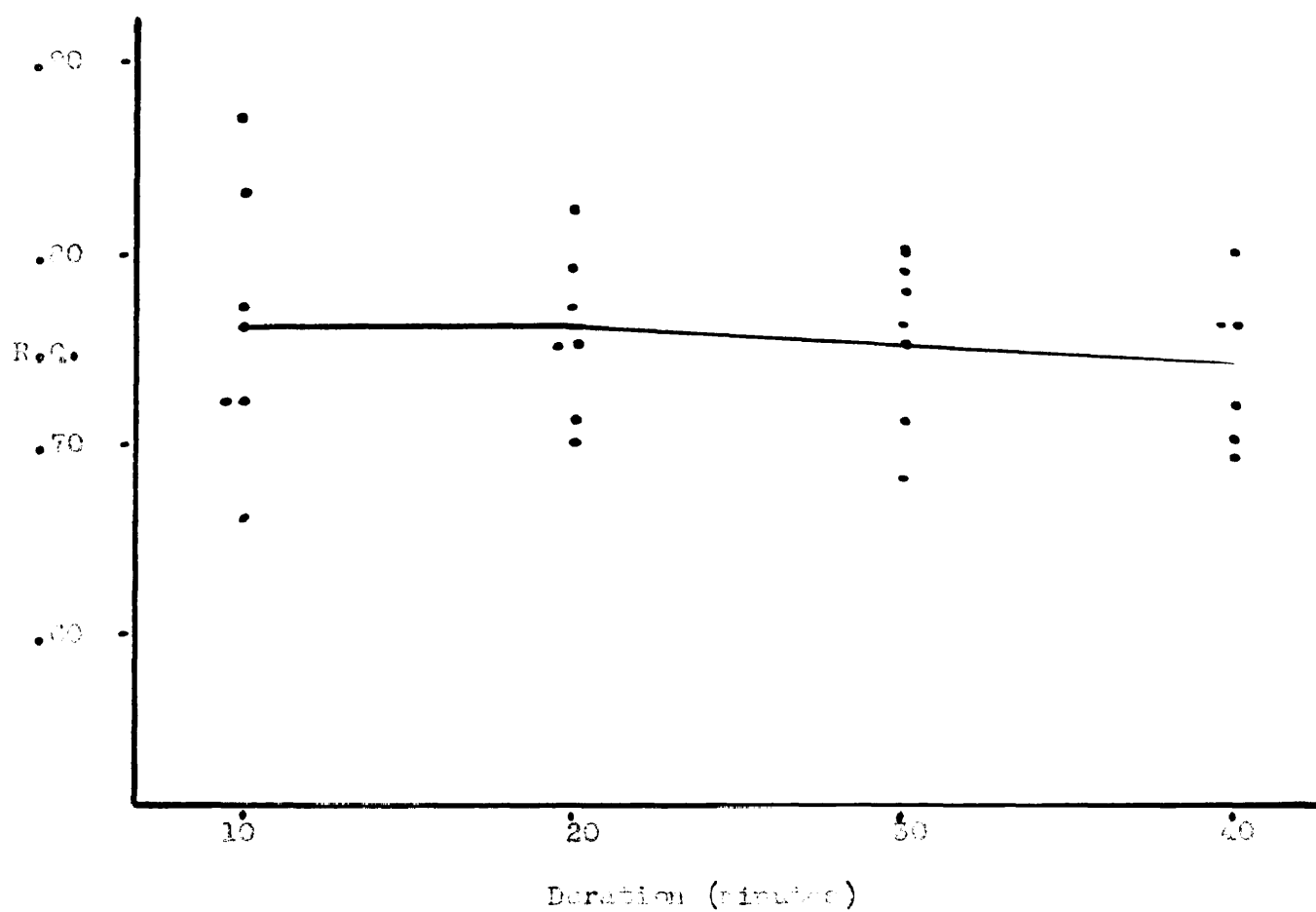


Dots represent individual determinations

Figure 7

Group B

The Cumulative Respiratory Quotients of Rats Breathing
in a Closed Chamber in Which the Expired CO_2
was Allowed to Accumulate

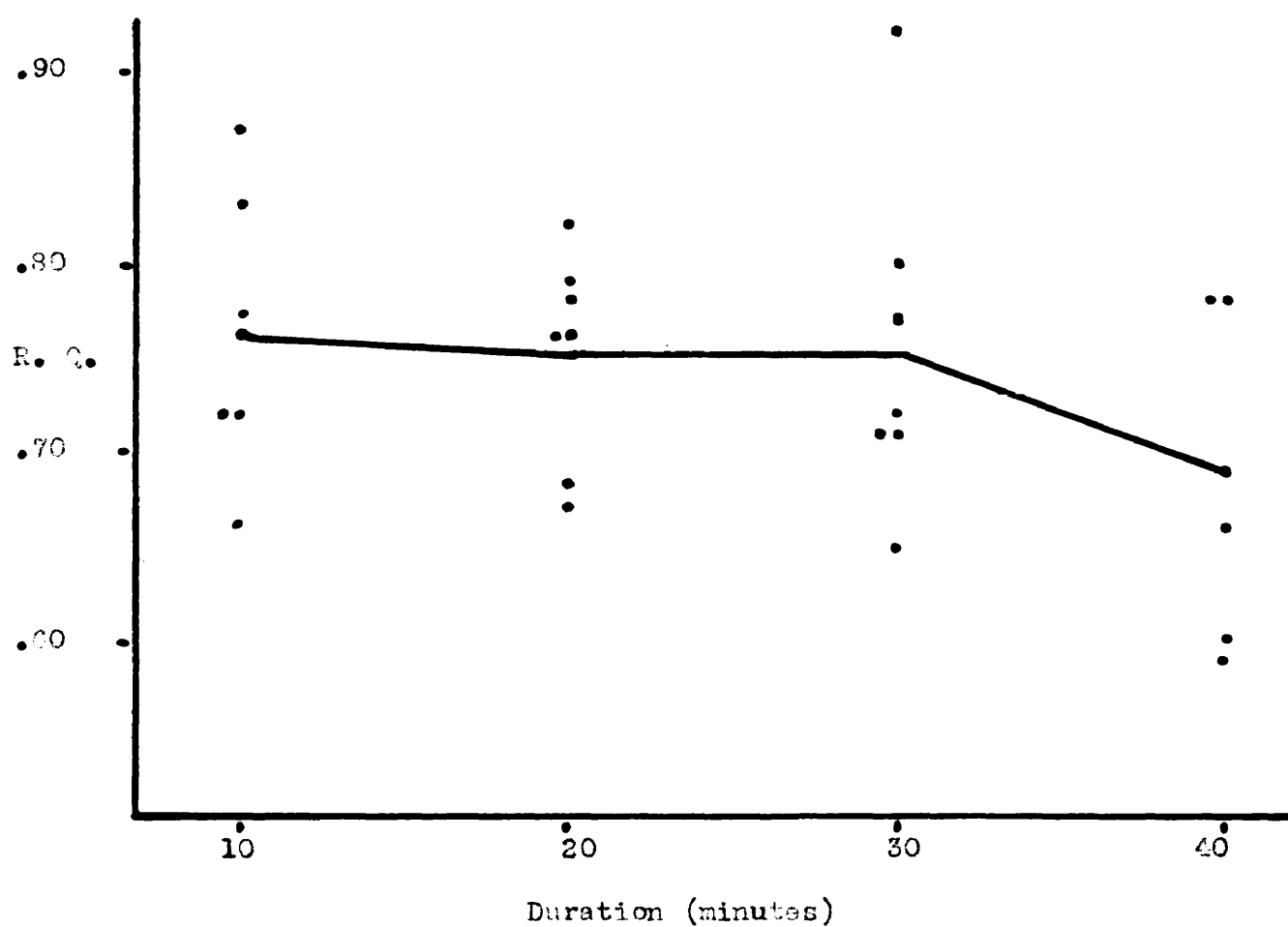


Dots represent individual determinations

Figure 8

Group D

The Period Respiratory Quotients of Rats Breathing in
a Closed Chamber in Which the Expired CO_2
was Allowed to Accumulate

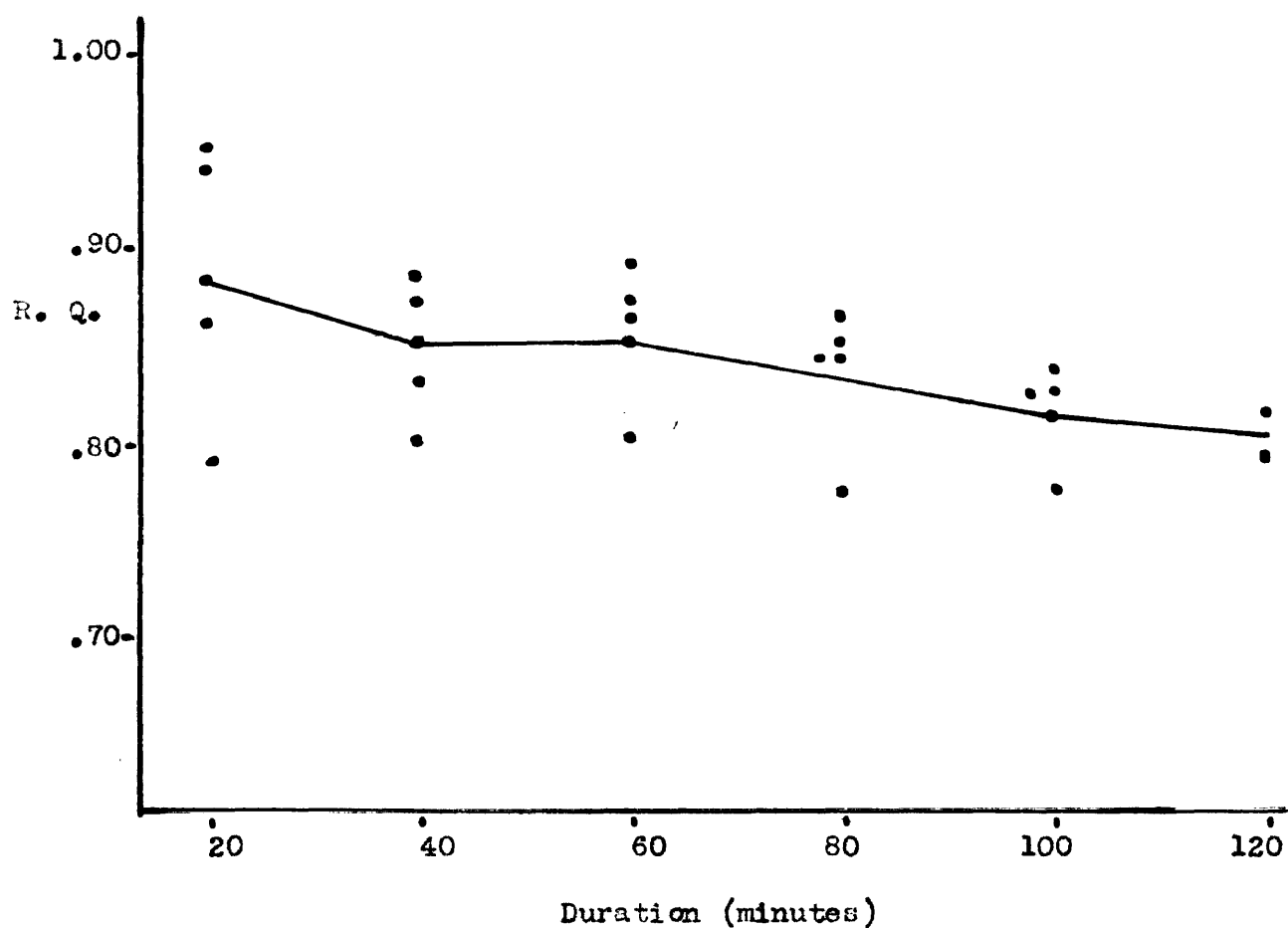


Dots represent individual determinations

Figure 9

Group E

The Accumulative Respiratory Quotients of Rats Breathing in
a Closed Chamber in Which Expired CO_2 was Allowed
to Accumulate

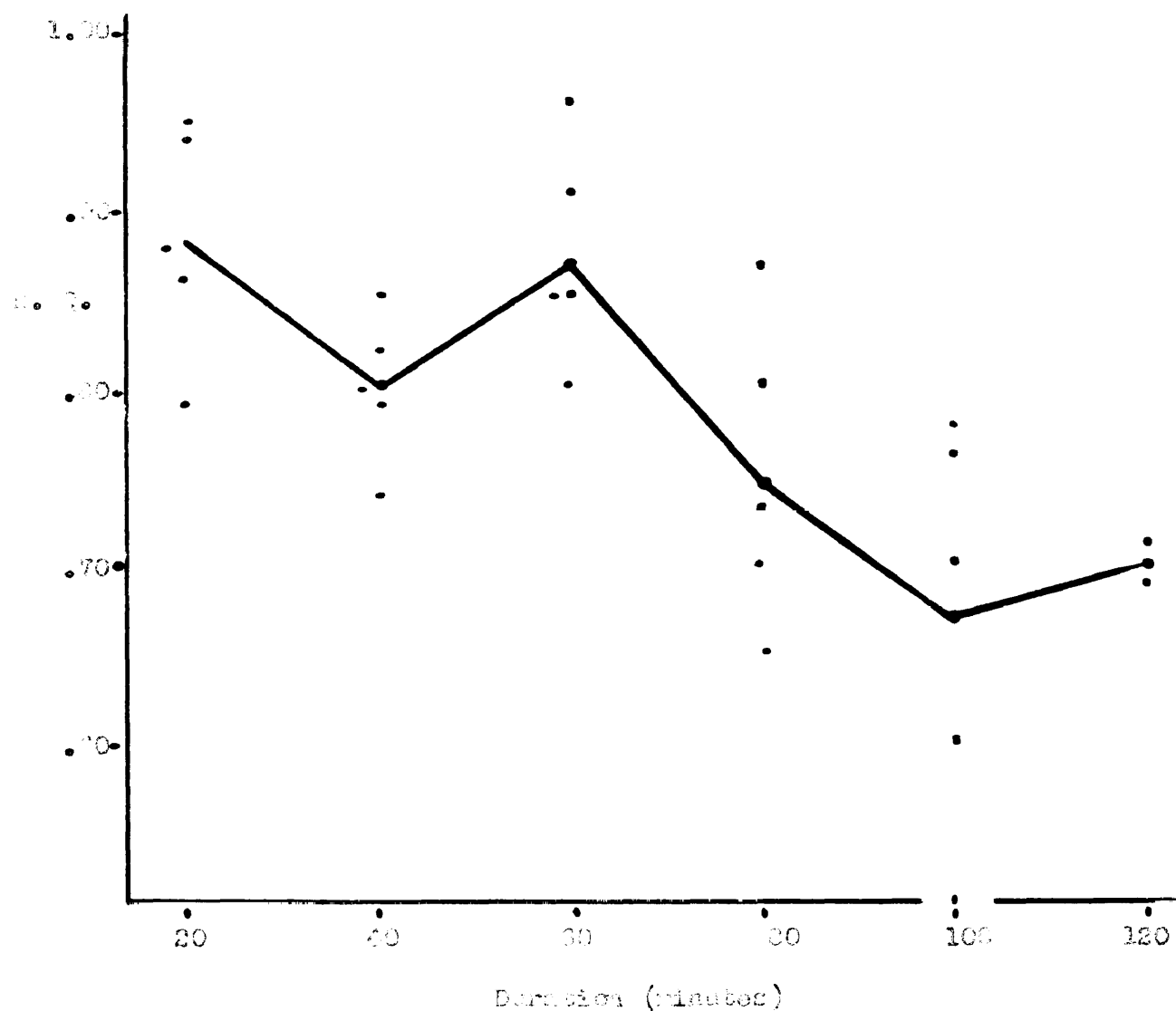


Dots represent individual determinations.

Figure 10

Group V

The Effect of a 100% Oxygen Atmosphere of Airway Breathing in
a Closed Chamber in Which Inspired CO_2 was
Allowed to Accumulate



Dots represent individual determinations.

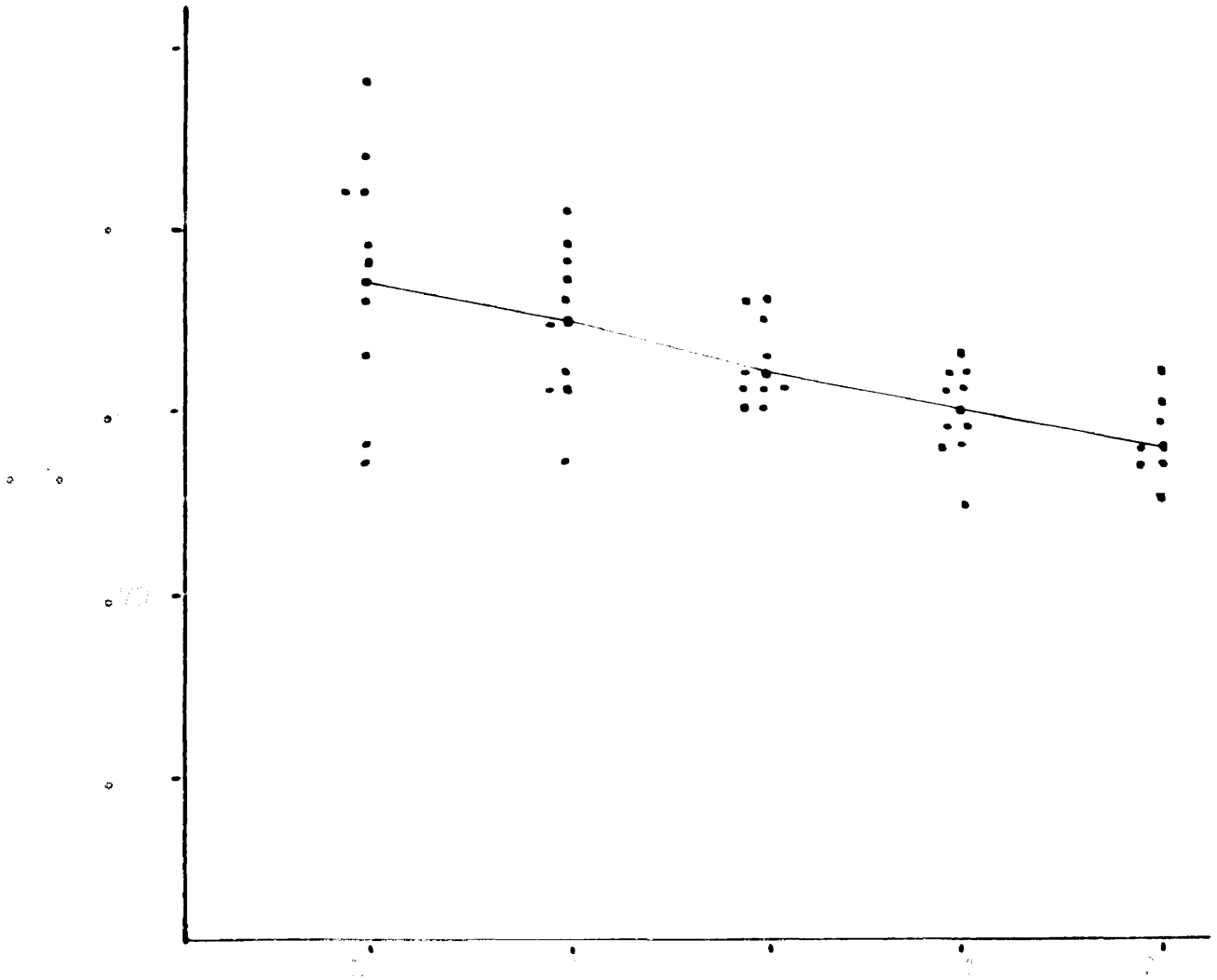
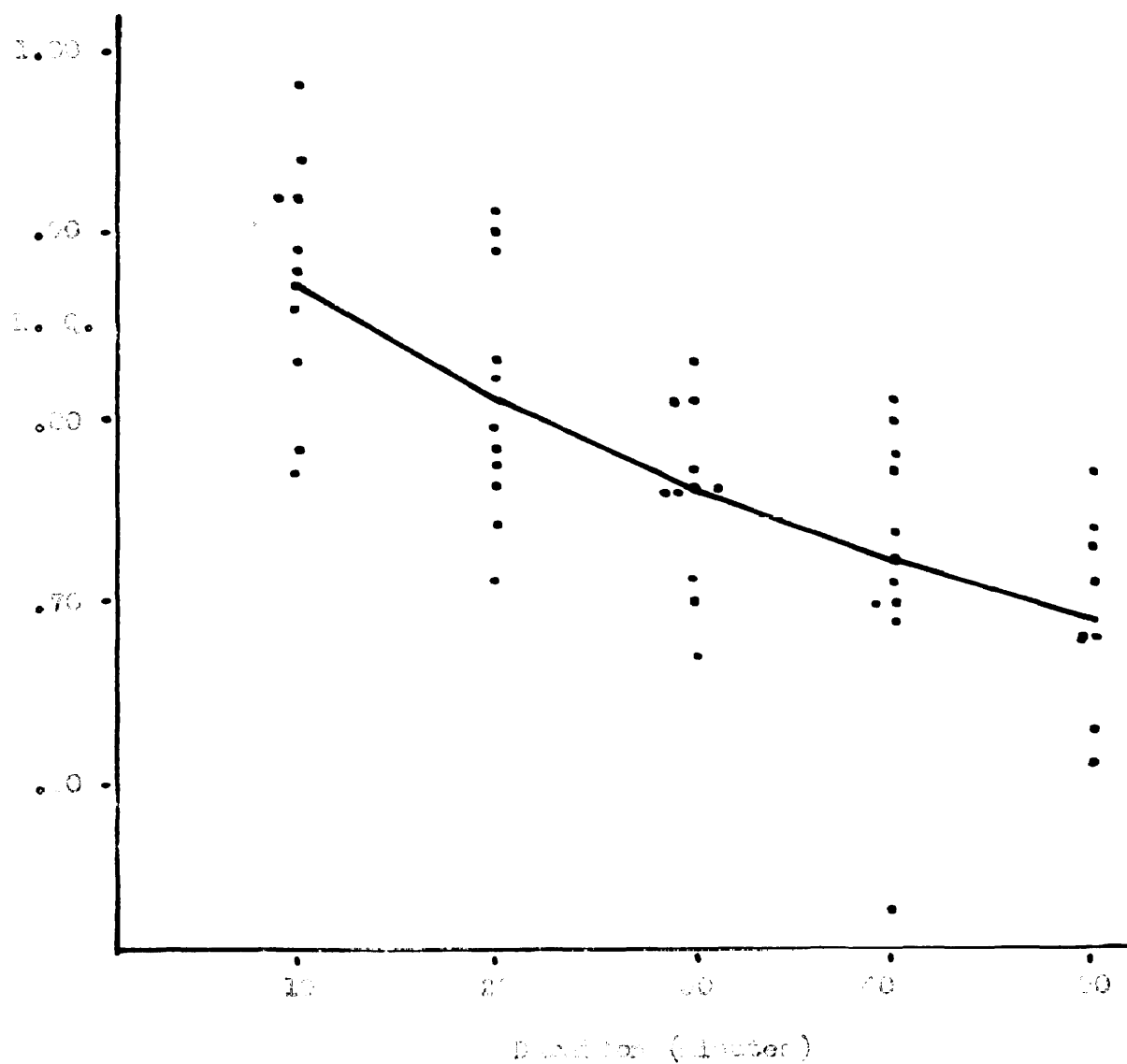


Figure 13

Figure 13

The critical concentration of water vapor in the air is a function of the relative humidity and the partial pressure of water vapor in the air.



Do not report individual experimental data

Figure 13

Group C

The Relationship of the Percentages of CO_2 and the
Respiratory Quotient of Mice

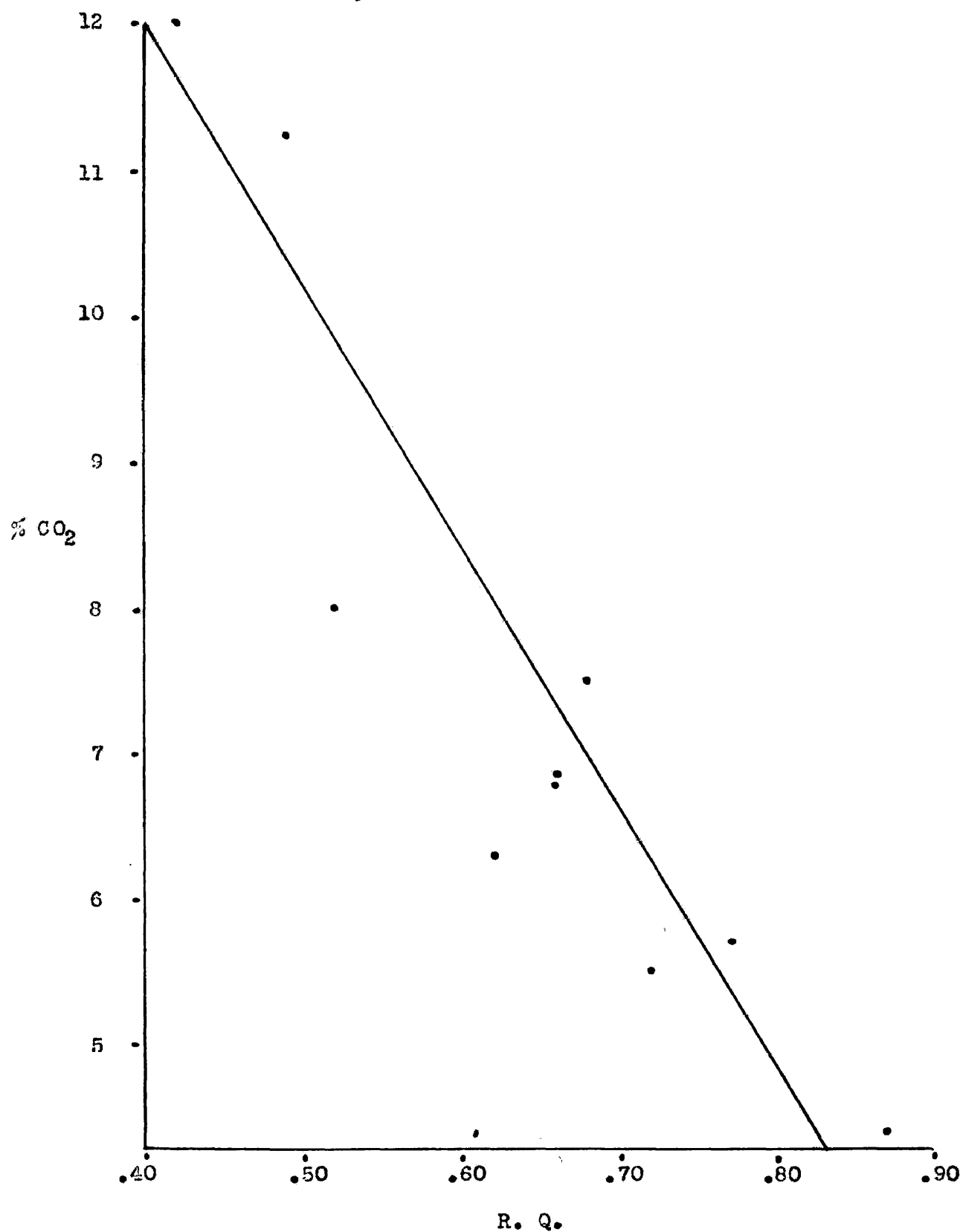
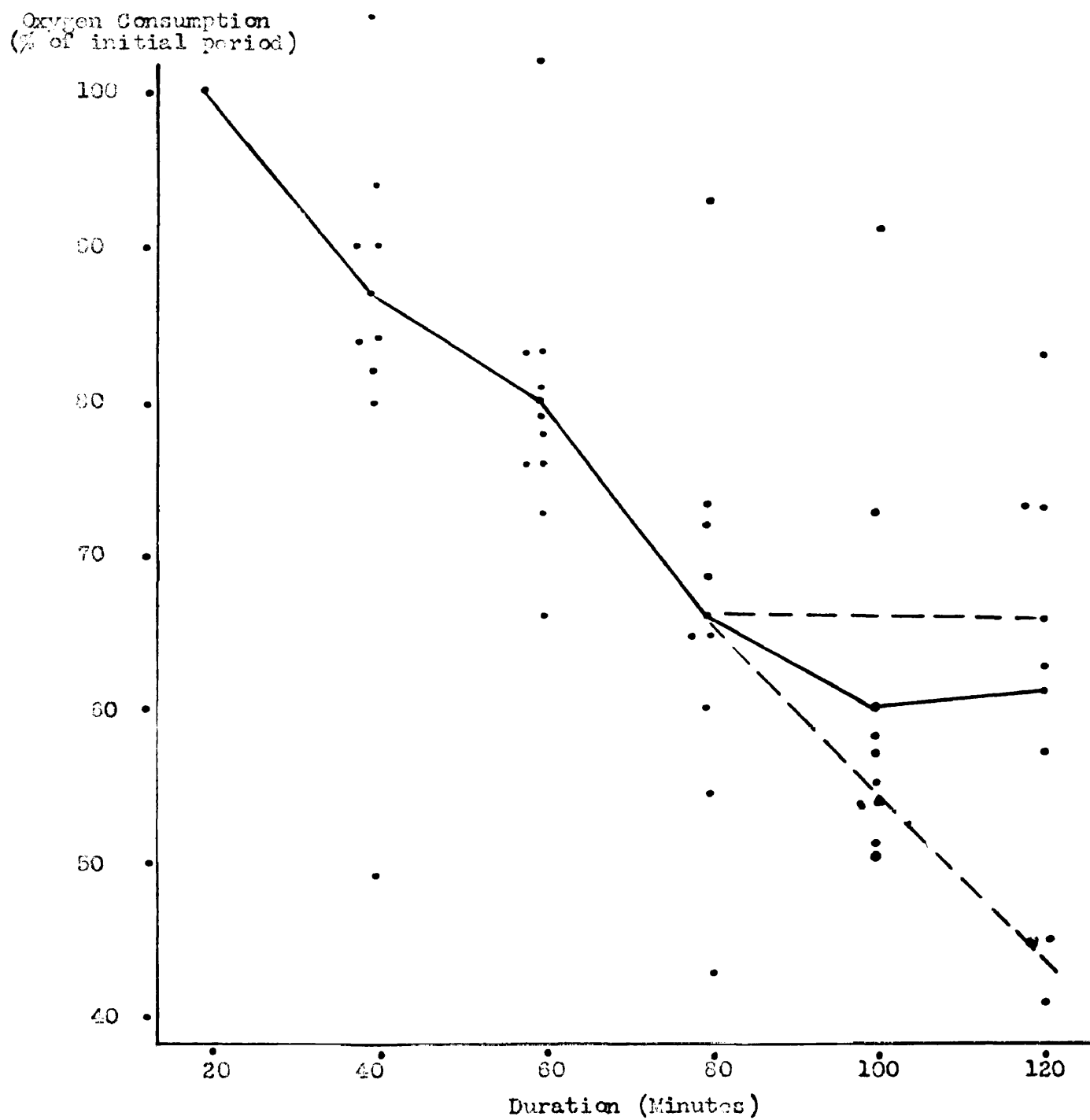


Figure 14

Group A

Oxygen Consumption of Mice Breathing in a Closed Chamber in Which Expired CO_2 was Allowed to Accumulate



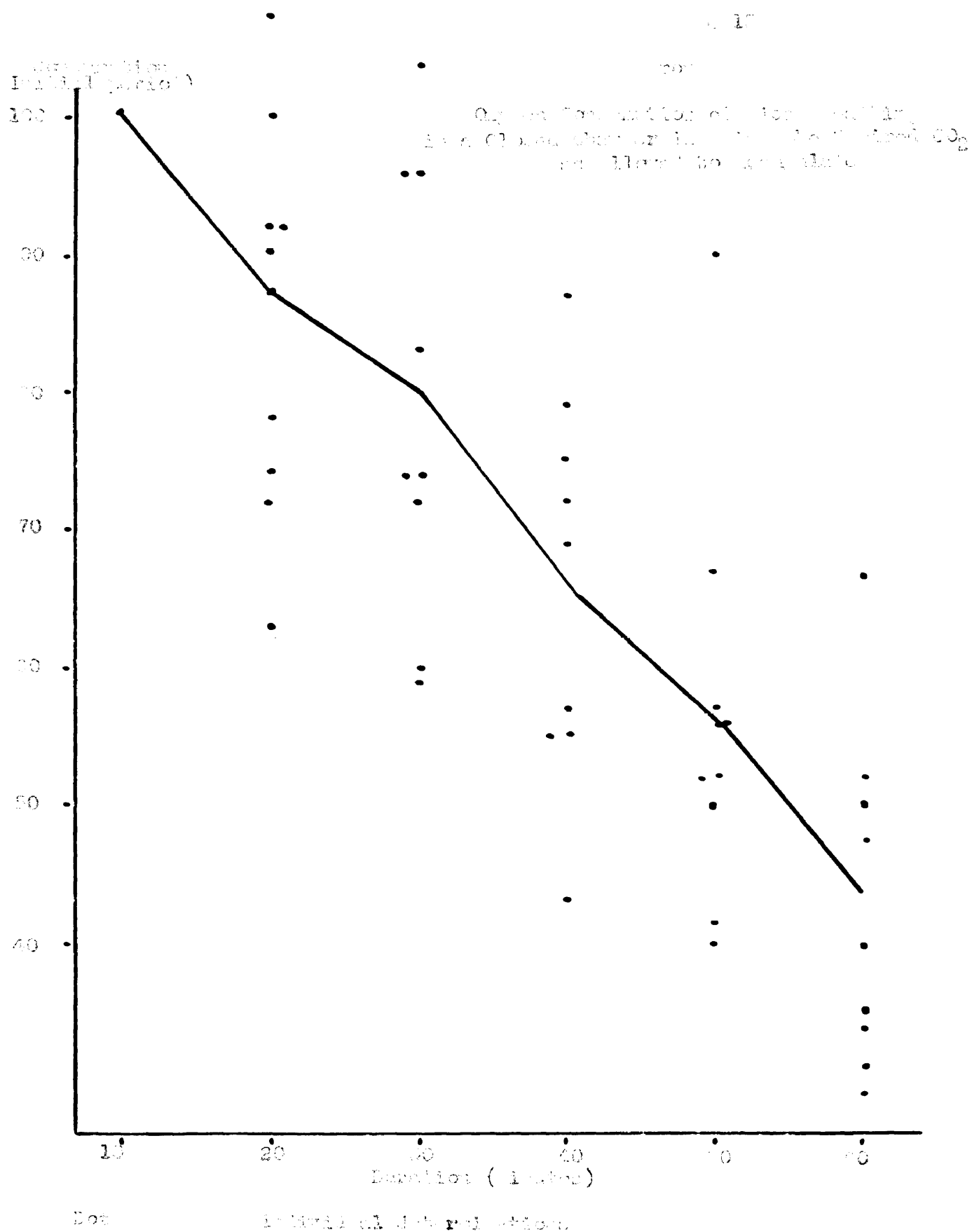
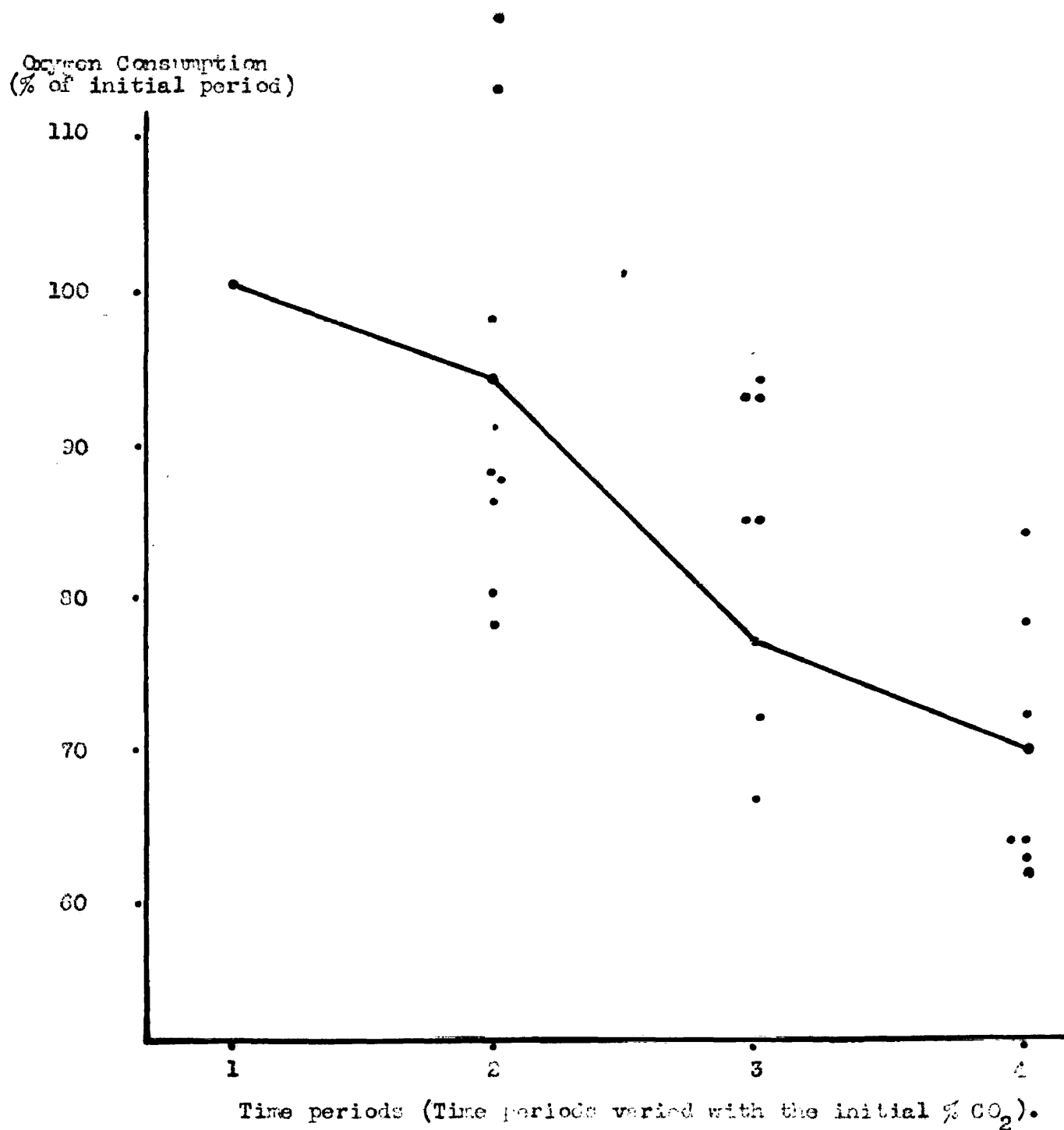


Figure 16

Group C

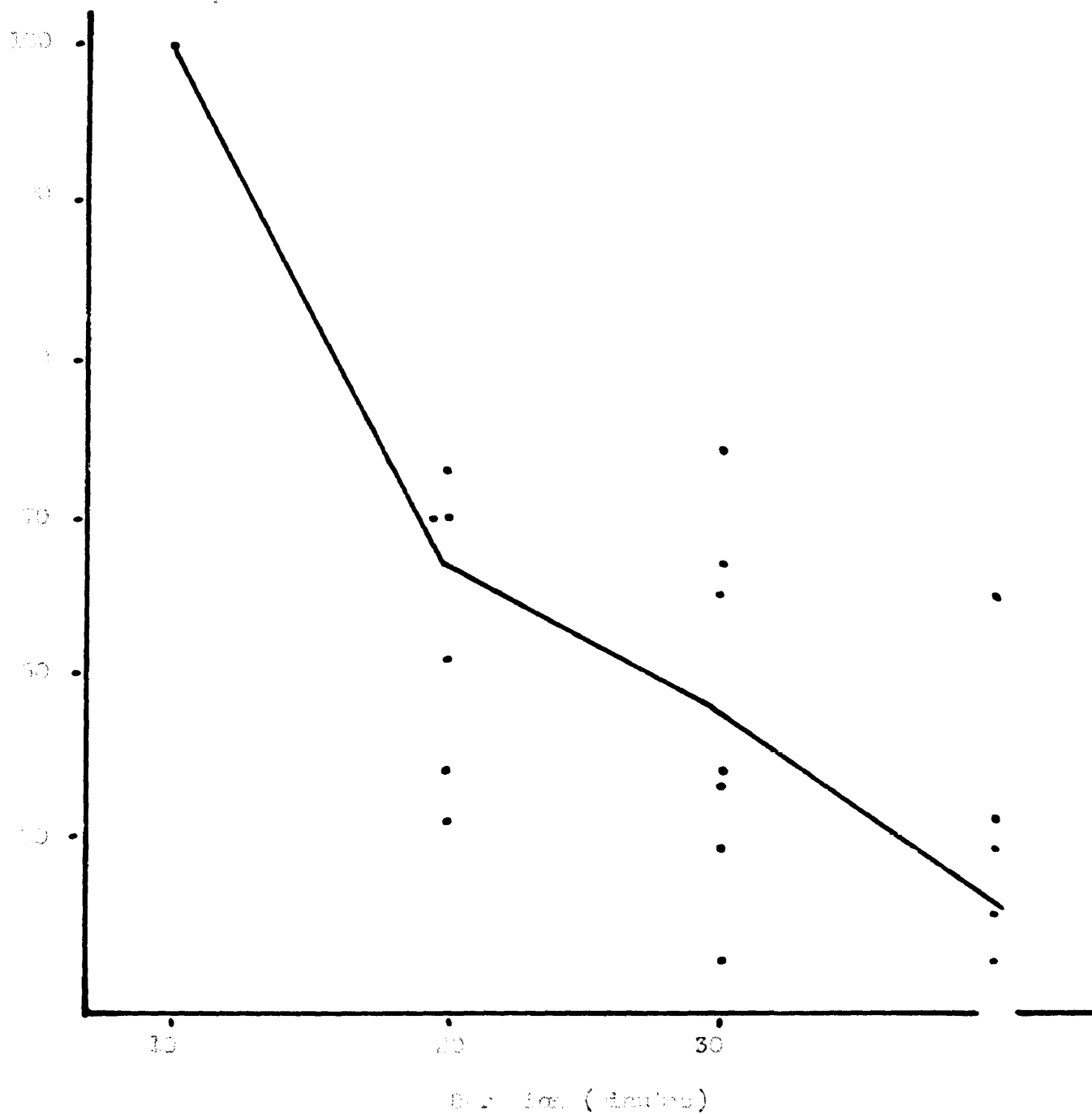
Oxygen Consumption of Mice Breathing in a Closed Chamber
in Which Expired CO_2 was Allowed to Accumulate. CO_2 Initially High



One determination at the third time period was .28, a value below the lower limit of the graph.

Calculation of the Breeding in a closed
 in 1971 and 1972 and allowed to accumulate

Survival
 (100 - initial value)



From

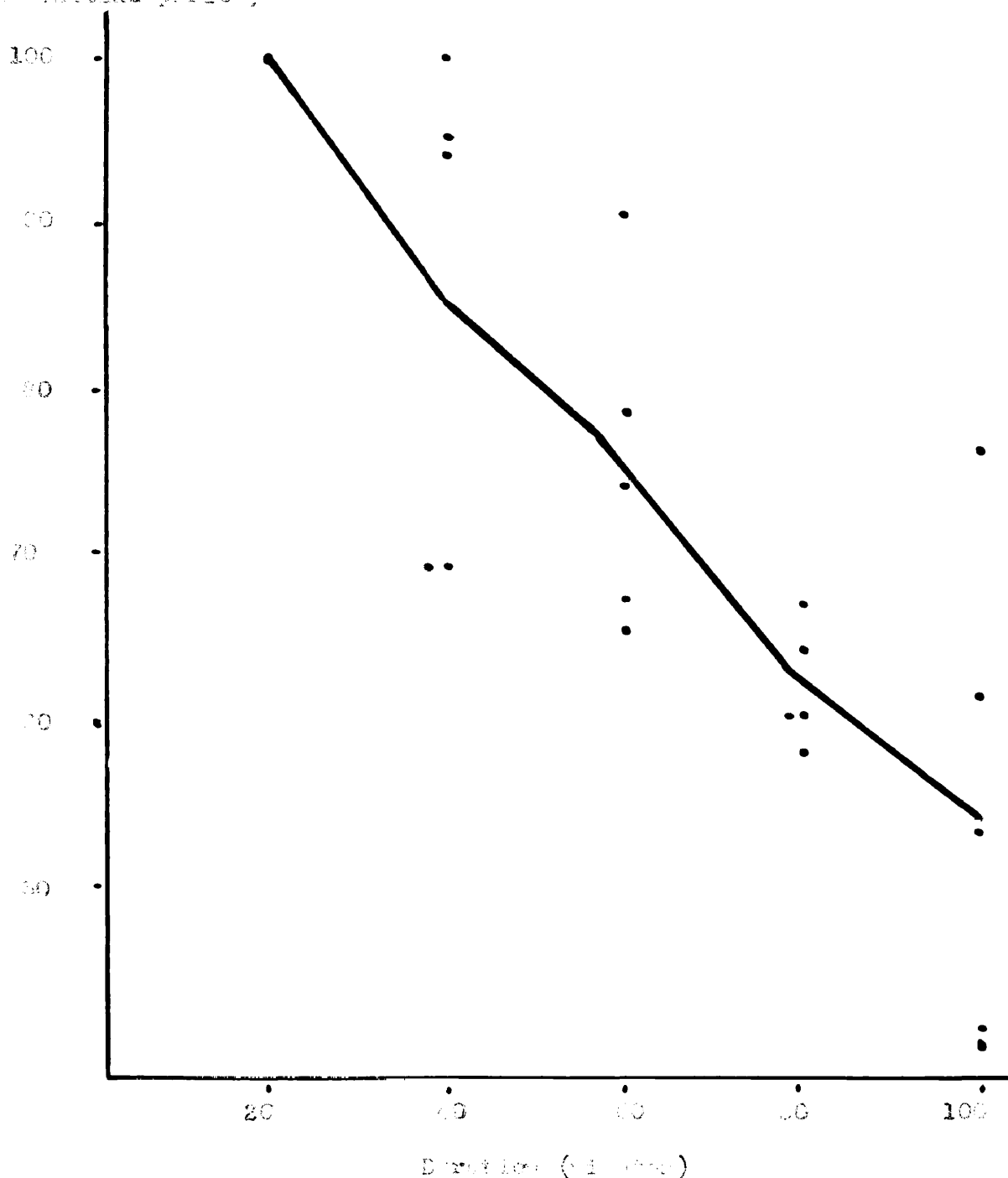
Initial value in lions

Figure 14

Group

per Consumption of Food (Ratio) in Closed Circuit
in Which Expired CO_2 was Allowed to Accumulate

Oxygen Consumption
(% of initial period)



Data presented in Figure 14 are from Group A

Figure 1

Group C

Effect on Consumption of Urane During Inhalation of CO_2 Rich
 Air and During Recovery While Inhaling Atmospheric Air
 (Average of 4 subjects)

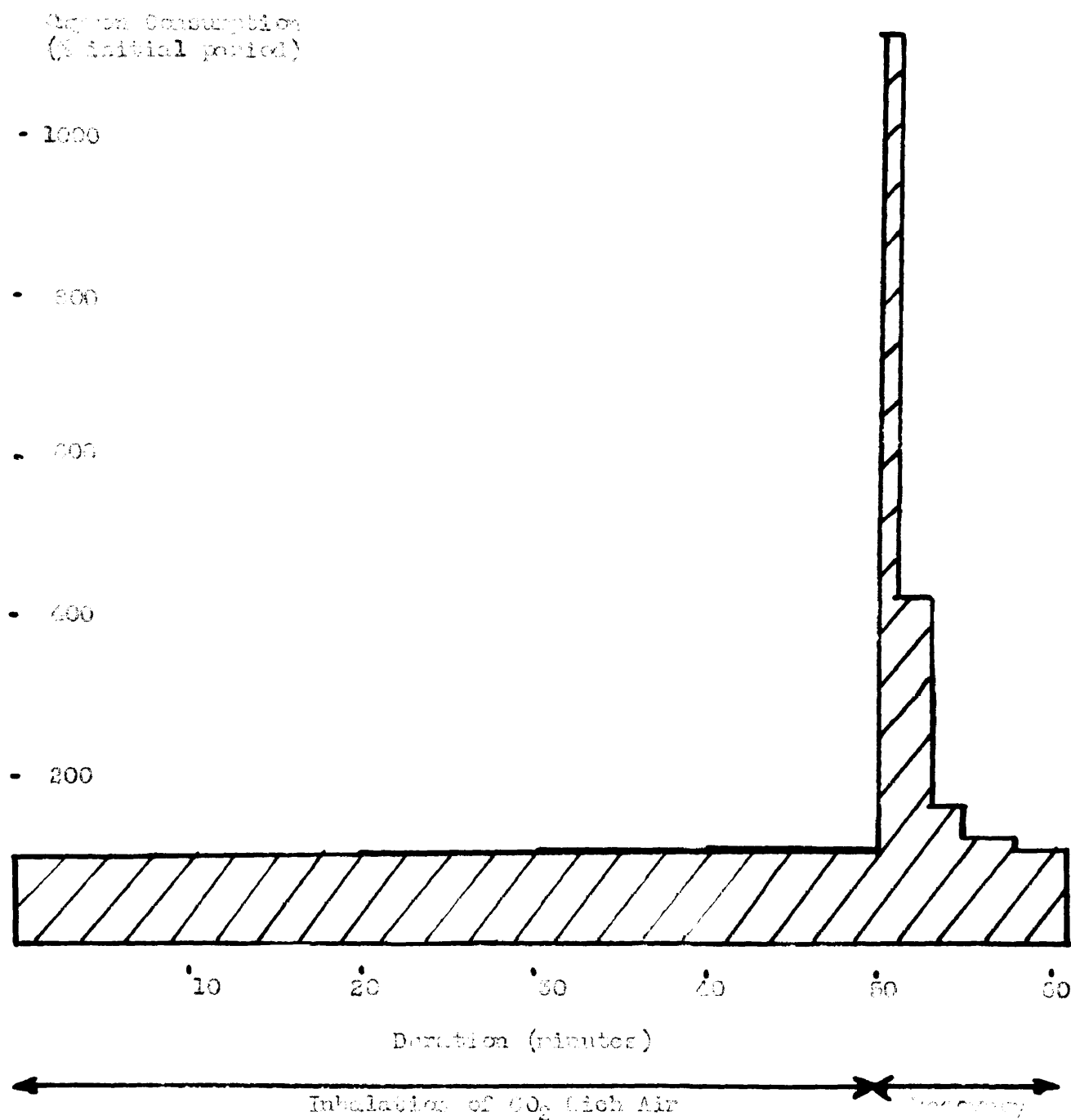


Figure 20

Group 3

Effect of Controlled and Semi-Controlled Inhalation of
 CO_2 Rich Air and During Recovery While
 Inhaling Atmospheric Air

(Average of 8 animals)

Oxygen Saturation
 (% of initial period)

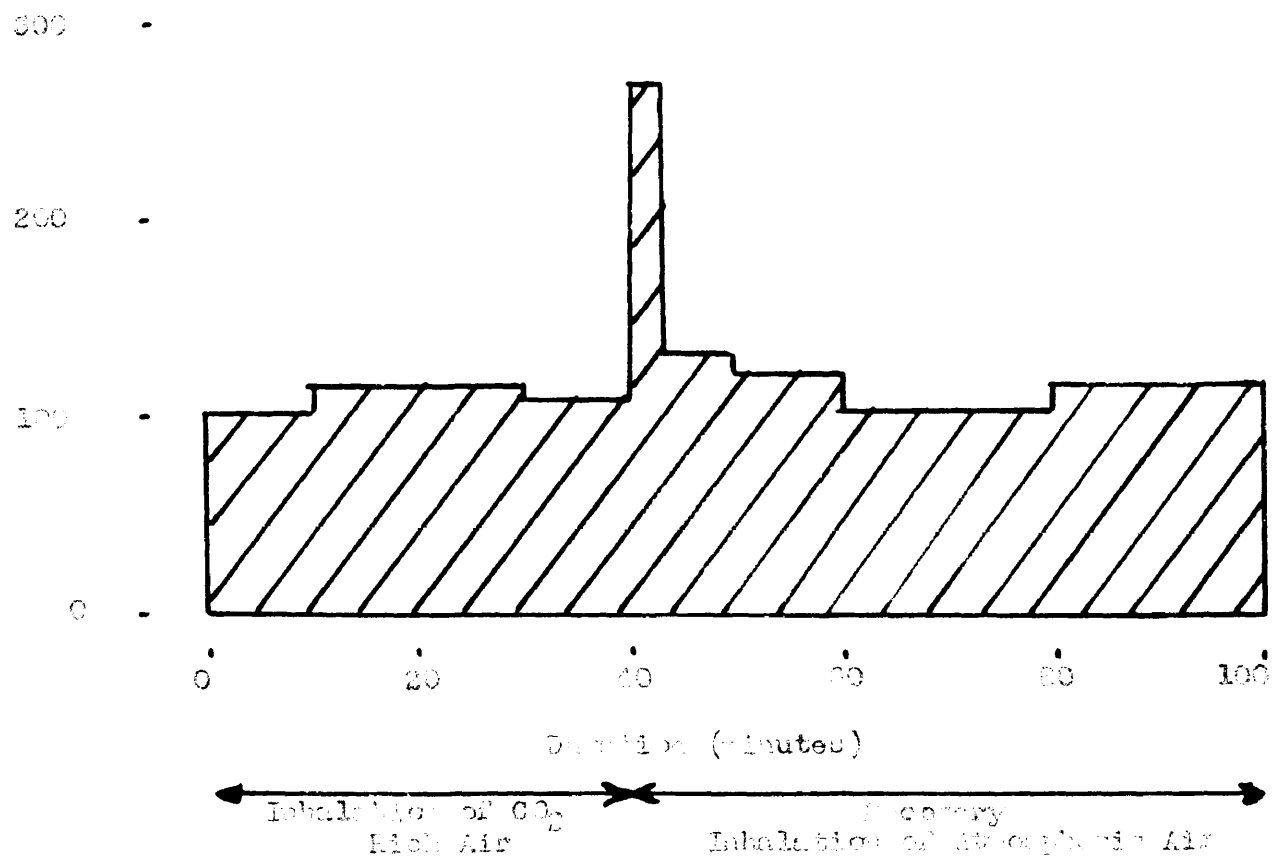
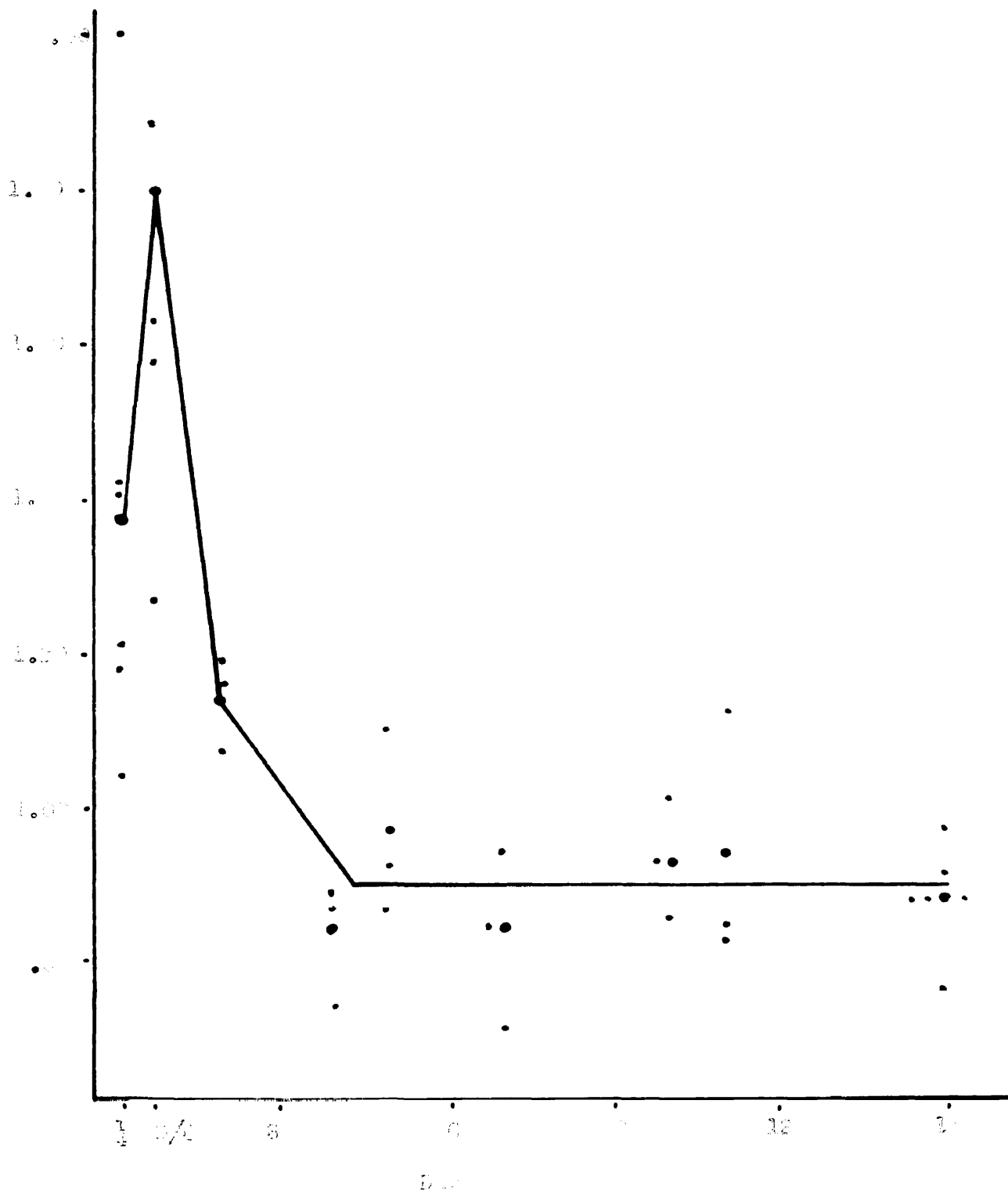


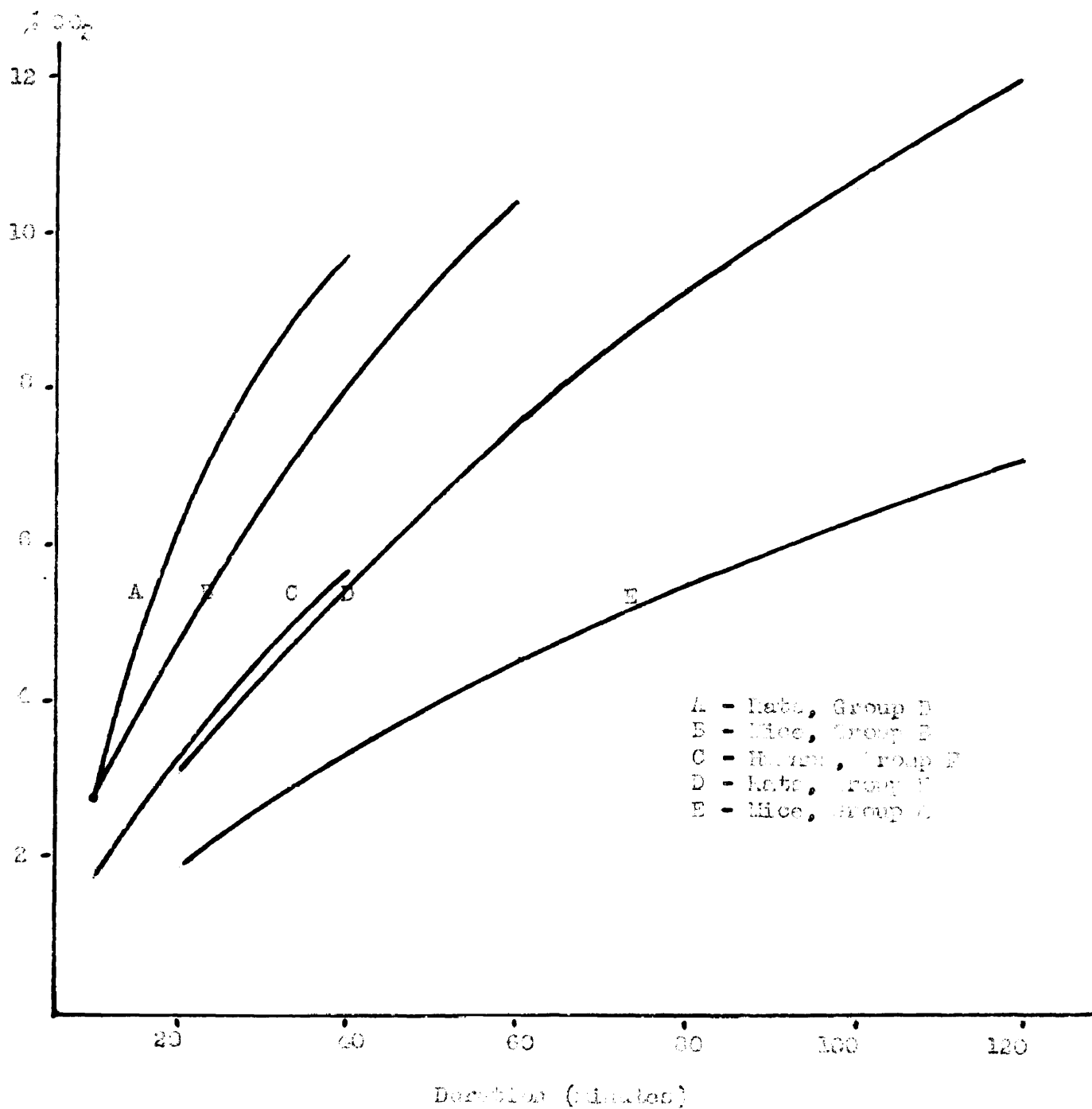
Fig. 21



Small number of
 data points for $x < 4$
 are dependent on x (see Fig. 7)
 for reliability of x (see Fig. 7)

Figure 22

CO₂ Increase With Time in Experiments with Rats,
Mice, and Humans Breathing Air From
Which Inspired CO₂ was ^{not} removed



DISCUSSION

The Effect of CO_2 on the Respiratory Quotient

The respiratory quotient is the ratio of the volume of CO_2 production to the volume of O_2 consumption. It is usually measured from the respiratory gaseous exchange. In ordinary determinations, the CO_2 production is measured as the CO_2 released from the body and collected in expired air samples. The oxygen consumption is similarly measured as the amount of oxygen removed from the inspired air. An R. Q. so calculated will be referred to in the following discussion as the "measured" R. Q. The "measured" R. Q. may not indicate accurately the actual CO_2 and O_2 changes produced during metabolism. If, for instance, oxygen could be stored in the body (and it apparently cannot) then the "measured" R. Q. would differ from the actual CO_2 and O_2 exchanges during metabolism because some of the oxygen used could have come from the stored oxygen and this amount would not appear in volumes measured as changes in respired gases. The R. Q. of the actual metabolism in the body will be referred to as the "true" R. Q.

Causes for Low "Measured" Respiratory Quotients. -- The observations on the animals and humans were made over periods of from 40 minutes to two hours. Phillips and White (59) demonstrated that the respiratory quotients of mice without food dropped slowly during the first six hours. This drop, however, was small in comparison to the decrease in the respiratory quotients observed in the present investigation. In the present experiments, the activity of the animals was not restricted and the only changes from a normal environment were an increased pCO_2 and a decreased pO_2 produced by the gaseous exchange of the animals. These changes,

then, must have accounted for the drop in the respiratory quotients. There are two possible ways in which the value of the CO_2/O_2 relationship could be lowered. One is by an increase in oxygen uptake; the other by a decrease in the carbon dioxide release of the animals. In mice and rats, the oxygen uptake, since it was decreased, could not have been the cause. Both mice and men experienced an immediate reduction in the R. Q. when inhaling air initially high in CO_2 when nearly normal levels (17-19%) of O_2 were present. This indicated, then, that the reduction in the R. Q. must have been due to a decreased release of CO_2 . The method of this reduction is discussed later under "Storage of CO_2 ".

Uniformly Low Respiratory Quotients. -- In all experiments, it was noted that the longer the animals or humans rebreathed the air, increasing the pCO_2 and thus decreasing the R. Q.'s, the closer the individual values were grouped around the mean. Breathing high CO_2 tended to bring the animals to a more uniform metabolic state. The wide range at the beginning of the experiments indicated dissimilar metabolic conditions of the animals. This establishing of a more uniform metabolic state was true for humans, mice and rats, and appears apparently to be a universal phenomenon in mammals. The drop in the R. Q., which was not the same for all animals, was due to the storage of carbon dioxide in the animal body. The drop was dependent upon the initial R. Q., which varied over a wide range depending on emotional state, diet, endocrine function, and degree of activity. Regardless of the initial R. Q., the values tended to reach a common level for all animals within a species.

The most logical explanation is as follows. As discussed below, only a part of the CO_2 stored in the bodies of animals and humans could have been buffered by the blood. Ferguson, et al. (24), suggested a labile

reserve of CO_2 in tissues sufficient to affect respiratory measurements in all animals with a changing acid base balance. From work with cats, they observed that only about ten percent of the 700 ml. of CO_2 stored in the body of the cat could have been stored in the blood. The remainder must have been handled by tissue buffers and equilibrium reactions. As indicated by a survey of the literature, numerous reports of investigators (12, 29, 47, 56, 76, 78) suggest that under appropriate conditions, CO_2 can enter into assimilation reactions in the body, i.e., the equilibrium reactions affecting the production of CO_2 can be partially, temporarily, or regionally reversed to incorporate CO_2 into members of the tricarboxylic acid cycle. It is suggested by the present author that this shift in equilibrium - due to assimilation reactions or simply to acid base shifts as a result of buffering - limited the type of food materials that could be burned, and thus produced the more uniform metabolic conditions of the animals. Since the oxidation of fats releases considerable energy by β -oxidation before CO_2 is produced by incorporation of compounds such as acetoacetic acid into the Kreb cycle, it is suggested that the drop in the R. Q. was not only due to storage of CO_2 in the body but also to increased oxidation of fats as the energy yielding fuel. Fats yield 6.628 cal/liter of CO_2 as compared to 5.047 cal/liter of CO_2 during carbohydrate oxidation. Hawley, et al. (35), suggested that in the oxidation of fatty acid chains, the uptake of O_2 may considerably outrun for a time the production of CO_2 . If there was a shift to fat metabolism, this could account for a further portion of the drop in the R. Q.'s observed.

<u>CO_2 per Calorie</u>	<u>R. Q. (Fuel)</u>
150.9 ml.	.707 (Fats)
198.1 ml.	1.00 (Carbohydrates)
171.0 ml.	.825 (Fat-carbohydrate mixture)
182.8 ml.	.90 (Fat-carbohydrate mixture)

The above table shows clearly that more energy is released per volume of CO_2 produced when fats are burned than when carbohydrates are the chief energy fuel. Tests for excess ketone bodies could have yielded data which would have settled this point. These tests were not run in this investigation.

The Effect of Breathing Initially High CO_2 . -- Since the above animals which rebreathed air for periods of from 40 minutes to two hours to produce pCO_2 sufficiently high to cause a drop in the R. Q. were subjected also to other changes (time and low O_2 tension) which could have been factors in the drop of the R. Q., both mice and men were subjected to rebreathing air initially high in pCO_2 which reduced to a minimum these two factors. The O_2 tensions were reduced but little from O_2 tensions in atmospheric air and the duration of exposure was only to the time of sampling, usually ten minutes. As indicated in Tables II and XIII and Figures 5 and 6, the initial R. Q.'s were below theoretical (.707) when the pCO_2 was high and in other cases were below normal. As pCO_2 increased, the period R. Q.'s fell abruptly to below the lowest theoretical value of .707. In mice, a linear relationship existed between the initial R. Q.'s and the initial pCO_2 s (Figure 13). The period R. Q.'s for mice rebreathing air initially high in CO_2 rose slowly. Under the conditions of this investigation, the rise occurred over the first 30 minutes. Later the R. Q.'s again fell. Nearly all R. Q. values were still below the lowest theoretical value, however. The slight rise in the R. Q. is explained as follows. When the animals were subjected to an atmosphere containing CO_2 higher than alveolar CO_2 , the animals stored most of the CO_2 produced causing low R. Q.'s. As pCO_2 in the tissues, blood, and alveolar air increased to above the pCO_2 of inspired air, the R. Q. rose due to release of CO_2 produced by metabolism.

It is suggested that the succeeding fall in the R. Q. can be explained on the basis of storage of CO_2 and shift toward fat metabolism as outlined above. Neither the rise nor the fall were statistically significant.

For rats in the smaller chamber (Figures 7 and 8), there was no statistical difference in the accumulative or period R. Q.'s. This was because the rats produced CO_2 rapidly enough to cause a drop in R. Q. even before the initial analysis. For an unexplained cause, the R. Q. drop for rats was not as great as the R. Q. drop for mice under the conditions of the present investigation.

R. Q. values have been plotted against time rather than pCO_2 . Figure 22 shows the relationship between CO_2 production and the duration of the experiments with rats, mice, and humans.

Effect of CO_2 on the Oxygen Consumption

In this investigation, it was observed that high CO_2 in the inspired air affected the metabolic rate, as measured by oxygen consumption, of some species of mammals. The oxygen consumptions were expressed as percentages of the oxygen consumptions of the first time periods. The volumes of O_2 consumption are presented in Tables VI, VII, VIII, IX, X, XI, and XII. The oxygen consumptions were expressed in this manner in the figures because the author felt that this represented a more equitable comparison of the oxygen consumptions of different individuals. Phillips and Goff (57) have found no uniform mathematical relationship between animal body weight and oxygen consumption in animals of similar sizes and ages. Further, they have found no uniform mathematical relationship between body weight and body surface area in mice. It is generally recognized that oxygen consumptions expressed on the basis of body surface rather than body weight constitute a more uniform mode of expressing and

comparing the oxygen consumption of different members of a species (3). Neither of these methods takes into consideration, however, the condition of the animals. An obese animal contains adipose tissue which metabolizes less rapidly than muscle or glandular tissue. Neither is the shape of the animal considered in these methods for species other than the human. For these reasons, the oxygen consumptions have been expressed as percentages of the initial time periods.

Phillips, Goff, and Bartlett (58) have demonstrated that mice and rats react to certain types of stresses by lowering the body temperature, and therefore, also the oxygen consumption. The scope of this response in larger mammals is not known. In the present investigation, the oxygen consumption of mice, rats, and humans were studied in response to breathing various concentrations of CO_2 .

Oxygen Consumption of Humans. -- Humans (Group F) responded to inhalation of CO_2 with a statistically non-significant increase in their oxygen consumptions. The cause for this slight increase was obviously the increased respiratory activity induced by inhalation of CO_2 rich air.

Oxygen Consumption of Mice and Rats. -- In contrast to the above response for humans, mice and rats responded with a sharp drop in O_2 consumption. Phillips and White (59) observed a significant drop in the oxygen consumption of mice kept without food or water for a period of six hours. The animals in the present investigation were observed, however, for a maximum period of two hours, and the drop in oxygen consumption was much greater than that reported by Phillips and White. It is evident, then, that some factor or factors in addition to time and lack of food and water were responsible for the fall in the R. Q.'s observed in the present series of experiments. Seever (66) reported that inhalation of 15% CO_2 mixtures produced a prolonged decrease in O_2

consumption in rats. Phillips, Goff and Bartlett (58) observed a drop in body temperature of mice and rats subjected to various forms of stresses such as caging and binding. In the present investigation, the body temperatures of the animals were taken at the beginning and end of the tests. In both mice and rats, there were drops in body temperatures (Table V). It is known that the metabolic rate may be proportional to body temperature in homeothermic animals. In this investigation, the drop in oxygen consumption of mice and rats was accompanied by a drop in body temperature.

Hypothalamic Control of Body Temperature and Metabolism. -- It is generally recognized that the hypothalamus controls the temperature of homeothermic animals either directly or by acting as a relay center for higher nerve centers. When a large animal, such as a human, is placed in a cold environment, the metabolic rate increases so that a constant body temperature is maintained. In contrast to this, Phillips, Goff, and Bartlett (58) have demonstrated that when mice were restricted by caging and placed in the cold, they rapidly lost body temperatures. In the present investigation, a drop in body temperature, which was accompanied by a drop in oxygen consumption, was observed when mice and rats were caused to inhale high CO_2 . The author suggests that both the drop of metabolic rate and body temperature observed in the present experiment were a result of a change in the hypothalamic control, since ordinarily basal metabolism is established at a level sufficient to maintain proper body temperature. The question is raised as to whether a drop in metabolic rate caused a drop in body temperature or whether a drop in body temperature caused a drop in metabolic rate.

According to the Q_{10} theory, a 10 degree drop in temperature should reduce the metabolism by approximately 50%. In these experiments, the

oxygen consumption was depressed an average of 50% but in no case did temperature drop equal 10°C. The averages were, in fact, less than 5°C. It is therefore evident that the drop in body temperature was not the cause of the drop in oxygen consumption (unless the $\dot{Q}_{10}$ value was more than 4 instead of approximately 2) because the latter was comparatively greater than the former on the basis of an average $\dot{Q}_{10}$ value of 2. It appears from this, then, that the hypothalamus controlled the level of metabolism and that as metabolism dropped, the body temperature dropped. In these experiments of comparatively short duration, the drop in body temperature lagged behind the drop in the metabolic rate for obvious physical reasons of heat dissipation. In summary, then, it appeared that the hypothalamic control (or loss of control) was responsible for the drop both in body temperature and in metabolism and that body temperature dropped as a result of the drop in metabolism.

Phillips, Goff, and Bartlett (58) have shown that drops in body temperature of mice is not the same under all forms of stress. It therefore appears that when temperature control is lost and body temperature and metabolism steadily drop, this loss of control also occurs in different degrees. This was demonstrated in the present investigation. The oxygen consumption of mice in the smaller chamber (Group B, Figure 15) dropped at twice the rate of the oxygen consumption of mice in the larger chamber (Group A, Figure 14). Also the rate of drop in oxygen consumption of rats in the smaller chamber (Group D, Figure 17) was more than five times that for rats in the larger chamber (Group E, Figure 18), over the first part of the experiments indicating clearly that when the hypothalamus lost temperature control (or permitted body temperature to fall) this loss of control occurred in different degrees.

There was also evidence in these experiments that the hypothalamus was able to change the rate of drop in oxygen consumption. In the graph for oxygen consumption for rats in the smaller chamber (Group D, Figure 17), a break is seen in the curve indicating a change in the rate of drop in metabolism. In the larger chamber (Group A, Figure 14), for mice where CO_2 increased slowly, the graph indicates that at 80 minutes, some of the animals were able to re-establish a level of control. As indicated by the hatched lines, some of the animals were able to maintain a constant metabolism at a lower level while the metabolic rate as measured by oxygen consumption of the other group of animals decreased at the rate established in the beginning of the experiment. This difference in responses is seen even at the 80 minute analysis by the large range and is clearly evident by the two separate distributions at 120 minutes. As mentioned above, it was impossible to use statistical treatment on the data of these responses. Even if additional animals showed no statistically significant divergent response, still, as evidenced by the total mean in Figure 14, there was a definite change in the slope of the curve representing oxygen consumption.

A comparison of the graphs for drop in oxygen consumption of mice (Figures 14, 15, 16) and rats (Figures 17, 18) with the graph for increase in pCO_2 (Figure 22) shows that the rate of drop in metabolic rate was roughly proportional to the rate of increase in pCO_2 . Most forms of stress such as binding or caging used to produce hypothermia are difficult to standardize, thus prohibiting accurate quantitative comparison of two different series of experiments. Since pCO_2 is easy to produce, to measure and to control, it is suggested that CO_2 as a stress for producing hypothermia could be used for the collection of quantitative as well as qualitative data.

pO₂ and Oxygen Consumption. -- Both pCO₂ and pO₂ changed as a result of rebreathing in the cases of men and animals (Tables XIV to XVI). All of the changes in oxygen consumption and in R. Q. have been attributed to changes in pCO₂. The possible role of pO₂ might well be suggested. A survey of the oxygen association curve of hemoglobin shows that pO₂ of 70-100 mm Hg produces nearly uniform (95%) saturation of hemoglobin with oxygen. In these series of experiments, pO₂ did not drop to 70% of atmospheric until the middle of the experiment and in many cases not until well into the latter half of the exposure. Also the high pCO₂ augmented breathing -- in humans, at least, where lung ventilation rate was measured -- so that even less than 14.7% (70% of atmosphere) of O₂ in inspired air would have caused nearly complete saturation of hemoglobin with oxygen. On the other hand, high CO₂ shifts the oxygen dissociation curve of hemoglobin to the right. This facilitates release of O₂ to the tissues and also inhibits the uptake of O₂ in the lungs. Since CO₂ seldom increased to over 10%, which would be about 76 mm Hg tension of CO₂ in alveolar air, neither increased release nor decreased uptake was of much importance in these experiments for the shape of the dissociation curve is not much altered at this pCO₂. It is therefore evident that low pO₂ could not have been the cause of the changes in oxygen consumptions or R. Q.'s on the basis of O₂ supply to the tissues.

"Recovery" From Inhalation of CO₂ Rich Air

From established curves, one can calculate the amount of CO₂ that can be carried by the blood. In the present series of experiments, as later discussed, much more CO₂ was retained in the bodies of the animals and humans than could be accounted for by blood buffering capacity. This extra must have been stored in tissues. There are several ways in which

CO₂ could have been stored in the tissues: (a) it could have been stored as buffered CO₂ in the blood, (b) it could have been stored by an inhibition of CO₂ producing cycles, (c) it could have been stored by incorporation into such compounds as members of the tricarboxylic acid cycle, or (d) it could have been excreted or secreted. It was believed that some hint as to the nature of the stored CO₂ could be obtained by following the course of the R. Q. during "recovery" from inhalation of CO₂ rich air while breathing atmospheric air.

"Recovery" and Respiratory Quotient. -- During recovery of both men and dogs, the initial respiratory quotients were below unity (Tables III and IV). In most of the experiments with humans, the first sample was drawn from expired air collected during the first 30 seconds of recovery. The R. Q.'s calculated from analysis of these samples were uniformly low - in no case approaching the value of .825 accepted as the standard R. Q. in the basal state in normal humans. In one test, when the first sample covered a two minute period, the initial R. Q. was higher: .85 as compared to an average of .76 for the one-half minute samples. The initial samples in the experiments with dogs was drawn from gases collected during a three minute period. The R. Q.'s of these samples were somewhat higher than those for the one-half minute period of humans. This is understandably so, since by the third minute, the R. Q.'s of humans were well above unity. The R. Q. values for the first three minute period of recovery for the dog, therefore, apparently represented an average of an initially low R. Q. and a high R. Q. which ensued within three minutes. After the first few minutes, the R. Q.'s were above unity. Following this, most R. Q.'s in the cases of both humans and dogs returned to a point below unity. This was not so in all cases, and hyperventilation

was undoubtedly the cause of the sustained high R. Q.'s in a few subjects. The R. Q.'s, of course, as measured by changes in respiratory gases, do not always reflect the true R. Q. If the dogs or humans were hyperventilating, the R. Q.'s would have been high and if they were hypoventilating, the R. Q.'s would have been low. Excitement or anxiety often is reflected in an increased pulmonary ventilation rate.

The rise of the R. Q.'s above unity during recovery was ascribed to release of the CO_2 which was stored in the body during inhalation of CO_2 rich air. The time of onset and the duration of the high R. Q.'s gave some indication as to the form of the stored CO_2 . An explanation of the low R. Q.'s during the first minute or so of recovery is discussed under repaying the O_2 debt which appears below. The rapidity of equilibration of CO_2 tensions between alveolar air and blood has been demonstrated. Any CO_2 stored as buffered CO_2 in the blood would be very quickly released from the blood as alveolar pCO_2 dropped on inhalation of normal atmospheric air. The R. Q. of humans had not, in all cases, returned to normal by ten minutes. The maintenance of an R. Q. above normal for this length of time indicated a source of CO_2 other than blood. That portion of the CO_2 stored in the tissues would be expected to be released from the body more slowly than that stored in the blood.

In Figure 21, which indicates the results of the experiments on humans, Group H, is shown the course of alveolar R. Q.'s during recovery. It is evident that the course of the alveolar R. Q.'s (Figure 21) did not follow the course of the R. Q.'s as measured from analysis of expired air (Table III). Alveolar samples collected at 15 seconds, 45 seconds, and at two minutes all indicated R. Q.'s above unity. During the same period of recovery, the R. Q.'s as calculated from analysis of expired gases indicated R. Q.'s below the accepted post absorption resting level

of .875. Alveolar samples were collected at the end of a forced expiration. The air thus sampled was air that would ordinarily have been a part of the functional residual air. This air, before being forced out of the lungs, was actually in the upper levels of the alveoli and thus in close approximation to the blood. CO_2 diffuses twenty times faster than O_2 . In ordinary R. Q. measurements, this difference in diffusion rates does not cause the alveolar R. Q. to deviate far from the R. Q. as calculated by analysis of expired gases. This is because pCO_2 of venous blood is about 6 mm Hg higher than pCO_2 in the lungs and only a limited amount can be released in equilibration in the lungs. When the pCO_2 of the blood, however, is much higher than that of alveolar air, as it was in the subjects of this investigation, then CO_2 release from the blood might well outrun O_2 absorption. O_2 absorption would be limited by the O_2 carrying capacity of the blood; CO_2 release would be limited only by the time the air and the blood were in close enough proximity for the exchange to occur. For this reason, then, the R. Q.'s of alveolar samples differed from the R. Q. as calculated by analysis of expired air. In ordinary metabolism, barring hyperventilation, the only CO_2 to be released from the body is that produced by metabolism. In these recovery experiments, there was the additional stored CO_2 to be released. When functional residual air was left in the lungs as in normal breathing, this release was slower than if the functional residual air were reduced by approximately half as it was in a forced expiration used for collection of alveolar samples.

In the case of the alveolar R. Q.'s, a plateau was reached at about five minutes and was maintained at an R. Q. of about .90 over the time the samples were collected (15 minutes). In about half of the

tests on humans and dogs when the R. Q.'s were calculated from analysis of expired gases, the R. Q.'s were still above unity at the end of ten or even 15 minutes. During this same time period, the alveolar R. Q.'s were practically all below unity. The reason for this difference in the alveolar R. Q.'s and expiration gas R. Q.'s is that during hyperventilation, excess CO₂ is blown off which would increase expiratory gas R. Q.'s more than alveolar R. Q.'s. As discussed below, some subjects were hyperventilating.

An R. Q. of .90 is above that expected of subjects under the conditions which existed in these experiments. This indicated, then, a slow release of CO₂ following the first excessive release which caused the high R. Q.'s of the first few minutes.

Repayment of the Oxygen Debt. — Karpevitch and Schneider (64) have divided the O₂ debt into two categories, the alactacid and the lactacid. The alactacid is paid much faster than is the lactacid and thus it is paid back first. The nature of this alactacid O₂ debt is unknown.

An O₂ debt would logically have been accumulated by the subjects inhaling CO₂ rich air since accumulated CO₂ interfered with normal lactic acid oxidation. The extent of this debt and the rate at which it was paid can be seen in Figure 19 (Group 6 for men) and Figure 20 (Group J for dogs). Figure 19 for humans shows the more detailed analysis of the oxygen debt recovery as samples were collected at smaller time intervals. The extent of the initial pay back was masked (Figure 20) in recovery of dogs because the first samples were collected during a three minute period. At some time near 10 minutes, as evidenced in Figures 19 and 20 by a return to an oxygen consumption near the oxygen consumption measured in the first period of rebreathing, the O₂ debt was repaid for

both men and dogs. The initial rapid consumption of O_2 probably indicated the payment of the alactacid O_2 debt. During this same time period, the R. Q.'s of expired air were low (Table IV for dogs and Table III for men). This would seem to indicate that the alactacid debt was represented by a substance of low R. Q. In the discussion of CO_2 storage, the author suggests that an increase of CO_2 in the blood and tissues might cause a shift to a higher percentage of fat metabolism. If this were so, excessive fat metabolism would have produced ketone bodies faster than the body could handle them, thus ketone bodies would have been accumulated during inhalation of CO_2 rich air. Even in exercise, there is considerable fat metabolism although carbohydrates appear to be the preferred fuel material (64). This fat metabolism in exercise could result in an accumulation of ketone bodies. Thus the alactacid debt observed in the present investigation could have been of the same nature as the alactacid debt accumulated during exercise.

Evidence in this present investigation would seem to support the contention that oxidation of accumulated ketone bodies represented the alactacid O_2 debt. Grollman (personal communication), from his work on the O_2 debt, suggested this possibility to the author. The first time period of recovery was characterized by excessive O_2 consumption and also a low R. Q. In light of the fact that the R. Q. would logically have been high as a result of the release of stored CO_2 , it is evident that the payment of this alactacid O_2 debt must have been due to the oxidation of a substance of low R. Q. It is therefore suggested by the author that the possibility of a shift toward fat metabolism during the inhalation of CO_2 rich air and the low R. Q.'s observed during the repayment of the alactacid O_2 debt strongly suggests that the alactacid

O₂ debt was represented by accumulated ketone bodies in these experiments. This might also be the nature of the alactacid O₂ debt measured by others.

The oxygen consumption of neither humans nor dogs was greatly affected by inhalation of CO₂ rich air. There was no decrease as in mice and rats, and ⁱⁿ many tests, there was a noticeable increase as a result of increased respiratory activity. In recovery, the oxygen consumption had dropped to nearly normal in 10 minutes for both men and dogs. From the evidence of these tests, it seemed that the O₂ debt was paid within 10-15 minutes while the release of CO₂ stored in the body during rebreathing of CO₂ rich air took a much longer time, as indicated by high R. Q.'s determined from expired air (Table IV for dogs and Table III for men).

In humans, the O₂ consumption during the payment of the alactacid O₂ debt ranged between 10 and 20 times normal O₂ consumption. This, according to Karpovitch and Schneider (64), approaches the limit of the ability of the blood and heart to supply O₂ to the body. A 13.3 fold increase in O₂ consumption has been recorded for a well trained individual. These subjects, then, were paying this debt as rapidly as the O₂ carrying capacity of the blood would permit. This further indicated the ease of oxidation of the substances which represented the alactacid O₂ debt.

Release of Stored CO₂. -- It was not possible to get quantitative data on the release of stored CO₂ during recovery. If some of the "stored" CO₂ had been actually excreted or secreted or if it had been part of an organic compound such as oxalacetate, this CO₂ would not have been recovered in expired air during the recovery period. In an endeavor to

determine the amount of CO_2 thus handled by the body, the author tested for this response in the experiments on Group C for men and Group J for dogs. For those subjects who did not obviously hyperventilate, thus blowing off additional CO_2 above that which was stored, it appeared that not all of the CO_2 stored was recovered in expired air. The effects of anesthesia and room temperature tended to induce a panting type of breathing in the unconscious dogs. This was marked in some dogs and the resultant hyperventilation was correlated with an elevated R. Q.

Because of the effects of the breathing pattern on the measured R. Q., it was not possible to obtain quantitative data on the recovery of CO_2 . It appears to the author that quantitative data will be acquired only when the problem is approached from another standpoint, i.e., when the CO_2 excreted, secreted, or incorporated into organic compounds is measured. Isotopic carbon could be utilized in such experimentations.

The accuracy of the Haldane-Henderson gas analysis apparatus was not sufficient to permit an accurate appraisal of the CO_2 release if this release occurred slowly over an extended period of time. For these several reasons, then, quantitative data were not collected for the rate of recovery of stored CO_2 . In summary, it appeared from the data collected that most of the released CO_2 was released in the first few minutes and that if there was a continued release, as the high R. Q.'s indicated, this release was slow and prolonged. It further appeared that not all of the stored CO_2 was released in normally breathing subjects.

Storage of CO_2

The measured R. Q. could differ from the true R. Q. either by changes in the O_2 consumption or CO_2 production. Measurement of O_2 consumption

is not subject to many errors. An O_2 debt in an organism or a possible storage of CO_2 could alter the measured R. Q.

Obviously, O_2 is not stored in any appreciable amounts but the true R. Q. would differ from the measured R. Q. if there were storage in the body or release of extra CO_2 from the body. Hyperventilation is known to raise the R. Q. incident to the blowing off of extra CO_2 from the bicarbonate of the blood (24). On the other hand, it is also possible that some of the CO_2 produced by metabolism could be stored in the body. This could occur, for instance, in three general ways: first, in being buffered by the blood or tissue buffers; second, by excretion as bicarbonate in the urine or pancreatic juice or perspiration, or during the secretion of HCl in the stomach; and third, if conditions were appropriate, it could be stored during a partial reversal of the Krebs cycle.

Calculation of CO_2 Storage. — If it is assumed that the type of food materials burned for energy release does not change during an experiment with rebreathing of air where CO_2 is allowed to accumulate, then the amount of CO_2 "stored" or retained in the animal body may be calculated from the relative amounts of CO_2 and O_2 . This assumption was made and therefore the measured R. Q. differed from the true R. Q. only by the storage of CO_2 . The difference, then, between what the volume of expired CO_2 would have been, had the R. Q. remained constant, and the volume of CO_2 found by analysis of expired air (used in calculating the "measured" R. Q.), represented the CO_2 retained in the animal body.

Table I shows the amounts of CO_2 stored in the body of mice, rats, and humans using this method of calculation. Before proceeding further with a discussion of the storage of CO_2 , it should be pointed out again that this method of calculation assumes a constant "true" R. Q., i.e., that the type of food materials burned did not change during the course

of the experiments. As mentioned earlier under discussion on the effects of CO_2 on the R. Q., there was the possibility that the increase in CO_2 might have forced a shift from predominantly carbohydrate to predominantly fat metabolism. This possibility was neglected in the calculations of "stored" CO_2 .

CO_2 Storage in Mice. -- The average amount of CO_2 stored in the body of mice whose average weight was 26.1 grams was 35 ml. If CO_2 buffering data for human blood are applicable to mouse blood, less than .5 ml. of CO_2 could have been buffered by the blood of each of these mice. This would have made the CO_2 content of the blood equal to the CO_2 capacity. Ferguson, et al. (24), have reported several factors which indicate a role of tissues in buffering or storage of CO_2 : (a) when rabbits were over-ventilated for $1\frac{1}{2}$ hours, an increase in the respiratory quotient was observed and on the basis of a uniform "true" R. Q. it was calculated that 250 ml. of extra CO_2 were blown off; (b) only a small portion of this could have come directly from the bicarbonate of the blood; (c) 700 ml. of CO_2 were retained by cats weighing 3 Kg. when they breathed air containing 7.5 percent CO_2 ; (d) blood buffering could have accounted for less than 10 percent of this storage; (e) bone and connective tissue took up carbonic acid; and (f) 2.5 ml. of CO_2 per gram were extracted by lowered pressure from mice which were eviscerated, skinned, and placed in a tube with acid. In view of these observations, Ferguson, et al. (24), suggested a labile reserve of CO_2 in tissues sufficient to affect respiration measurements. Rosenbaum (61) maintained that a portion of the CO_2 released during hyperventilation in humans was given up by the tissues.

As discussed below, more CO_2 was stored in the bodies of mice in the present investigation than could be accounted for even in view of the

large tissue reserve suggested above. The above references do, however, indicate the importance of tissue storage and reserves of CO_2 which were doubtless factors in the storage observed in the present experiment.

Rate of CO_2 Storage. -- It seems evident from the data that CO_2 storage is not only a function of $p\text{CO}_2$ in the inspired air but also a function of time. The importance of time is evident in a comparison of the CO_2 retention (Table I) for mice in the 2,778 ml. chamber (Group A) and mice in the 955 ml. chamber (Group B). Although percent CO_2 in the smaller chamber increased to 10.3 as compared to 7.1 in the larger chamber, the amounts of CO_2 stored by mice in the smaller chamber were less than one-half of that stored by mice in the larger chamber. The duration of each test was two hours in the larger chamber (Group A) and one hour in the smaller chamber (Group B). A comparison of the two groups of experiments with rats (Table I, Groups D and E) shows a similar relationship, i.e., that those rebreathing the longer time stored correspondingly more CO_2 .

Buffering Action of Blood and Storage of CO_2 . -- The amount of CO_2 transported by the blood varies with CO_2 tension in the tissues and alveolar air. Karpovitch and Schneider (54) reported that CO_2 production produces a maximum of 75 mm Hg pressure of CO_2 in the tissues during strenuous exercise. In the present investigation, the activity of humans was only slightly increased and the metabolism of the animals was decreased. On the basis of metabolic rate, then, the production of CO_2 should not have been much, if at all, above normal resting levels. As CO_2 in inspiratory air increased to and above venous CO_2 , then $p\text{CO}_2$ in the venous blood increased and this then would have caused a

corresponding rise in $p\text{CO}_2$ in the tissues. CO_2 is 20 times more diffusible than O_2 and equilibration is made very rapidly in the lungs, between alveolar air and blood. This indicates, then that $p\text{CO}_2$ in the tissues was only slightly higher than $p\text{CO}_2$ in the alveolar air. Knowing this, the CO_2 combining power of the blood as it passed through the tissues can be calculated. The following calculations are based on the dissociation curve for reduced blood. The dissociation curve for oxygenated blood indicates smaller values for CO_2 combining power.

CO_2 in inspired air for humans increased to about 7%. Neglecting the pressure of water vapor, $p\text{CO}_2$ in inspired air reached a high level of 53.2 mm Hg. If $p\text{CO}_2$ in the tissue and venous blood varied 10 mm Hg from this value, $p\text{CO}_2$ in the venous blood was 63.2 mm Hg. References to curves constructed by Van Slyke as shown in Henderson (38), indicates that normal human blood when exposed to 40 mm Hg pressure can carry 55.5 vol. % CO_2 ; and that normal human blood at 63.2 mm Hg can carry 64 vol. % CO_2 . This is an increase of 8.5 vol. %. Blood capacity of an average man would not exceed 6,500 ml. The additional amount then of CO_2 which could have been carried by the blood of humans under the conditions of the present experiment, was 8.5×65 or 552 ml. of CO_2 .

Table I indicates that in only one test with humans was stored CO_2 less than 552 ml. CO_2 storage in humans, with the exception of the abovementioned test, varied between 830 ml. to 3,840 ml. of CO_2 . These values were recorded at about 760 mm Hg and at 22°C so actual values are a little lower (less than 10% lower). The amount of CO_2 stored above 552 ml. must be accounted for, therefore, in storage reserves other than blood.

CO_2 stored in mice and rats demonstrated even a lesser role for blood buffers. In Group A, the CO_2 stored in the mice averaged 35 ml. The

weight of the mice averaged 26.1 grams. These mice could not have contained over 5 ml. of blood each. CO_2 in inspired air reached a maximum of 7.13% or 54.4 mm Hg. This is neglecting water vapor pressure.

Assuming a 10 mm Hg differential (which seems high) between alveolar air and tissue fluid, the pCO_2 in tissue fluid and venous blood was 64.4 mm Hg. This is an increase in association of CO_2 and unoxygenated blood of less than 9 vol. % at 40 mm Hg CO_2 tension. Excess CO_2 that could have been buffered by the blood of the mice was less than .5 ml. Most, then, of the CO_2 was stored elsewhere in the body. The above calculation for mice is based on data for human blood as reported by Henderson (38).

Similar calculations of Groups B, D, and E (Table I) indicated with mice and rats the correspondingly small role played by the blood in storage of CO_2 . Ferguson (24) reported that of the 700 ml. of CO_2 stored in cats weighing 3 Kg., less than 10% could be accounted for by blood storage. These figures seem high according to the above calculation which indicates that about 30 ml. of CO_2 could have been stored in the blood of cats of this size. Dantcheff, et al. (18), claimed that frogs retained CO_2 by increase in alkaline reserve. Any storage of CO_2 in the blood which did not alter the pH would increase the alkaline reserve.

pH Drop and Possible CO_2 Storage in Tissues. — Spencer, et al. (72), have reported that each increment of 10% increase in the CO_2 concentration results in .2 unit drop in pH of the blood. CO_2 in the present investigation increased to 5-10% thus pH drop would have been .1 to .2 units if this data for dogs is applicable to mice and humans. The pH drop must be approximately the same in the tissues as in the blood. A pH drop in the tissues could have inhibited the production of acid metabolites such as CO_2 and lactic acid by interfering with equilibrium reactions. This could have been a partial cause of the decrease in O_2 consumption.

The buffering capacity of tissues is doubtless lower than the buffering capacity of the blood which is specialized for this function. If tissues were as effective in buffering acids as the blood, it is interesting to speculate on the amount of CO_2 that could be so buffered. In a 25 gram mouse, it would not equal more than 2.5 ml. of CO_2 . As indicated from the data in Table I, this was only a small portion of the CO_2 stored in the bodies of mice in Group A. The most logical explanation for the storage of remaining CO_2 is in disturbed equilibria; or excretion in saliva, perspiration, or urine; or there remains another possibility. Kretschmer und Wessel (43) reported that baths in water having a high CO_2 content increased, by 6 mm Hg, the CO_2 tension of alveolar air and also increased the alkaline reserve of the blood. They claimed that the effects of the baths must be explained as an intake by the skin. If such an intake is possible, then CO_2 diffusion out through moist skin is also a possibility, and might partially account for the "stored" CO_2 .

Tissue buffers, if as extensive as blood buffers, could account for all the stored CO_2 in man. The same is true for rats in Group D. For mice in Groups A and B and for rats in Group E, it is seen that tissue buffers as extensive as blood buffers could not account for all the CO_2 stored in the body.

CO_2 Storage in the Krebs Cycle. -- Miller (54) in a study of acclimatization of dogs to CO_2 , observed that there was an increase in the red cell count and also in the percent hemoglobin. He also noted an increased reticulocyte count. He concluded that the bone marrow stimulation was due to a tissue anoxia resulting from a depression of tissue oxidation caused by high CO_2 . This conclusion suggests to the present author that

inhalation of high CO_2 inhibits the release of CO_2 from the body to the point where the accumulated CO_2 inhibits the release of energy by reversing, or at least changing, equilibrium reactions in the body. Several investigations have been carried out on the fate of CO_2 in the animal body and on the fixation of CO_2 in vitro. CO_2 has been found incorporated into such compounds as oxaloacetate (76), carbonyl compounds (12), α -keto glutamic acid (47), and 2 malic acid from pyruvic acid (56). Other investigators have studied the mechanism of the fixation of CO_2 in the Krebs cycle. Such work up to 1946 has been reviewed by Wood (78). Studies directed by the Brookhaven National Laboratory (29) have demonstrated the possibility of reversal reactions with the incorporation of CO_2 into members of the tricarboxylic acid cycle at nearly every step in a series of reactions which ordinarily result in the release of CO_2 . The incorporation of CO_2 in the cycle does not necessarily indicate the complete failure of that cycle as an energy producing mechanism for normal metabolism. All reactions of the tricarboxylic acid cycle are reversible reactions and a shift in equilibrium in a localized area could result in the incorporation of CO_2 into some members of the cycle without affecting the overall functioning of the cycle. This type of regional reversal might occur in a brief space of time in a localized area of active muscle tissue, for instance, without affecting even the total energy release in the muscle. This idea, then, does not necessitate a new conception of energy production in mammals but only a re-interpretation of the metabolism of CO_2 in the light of equilibrium reactions. It should also be pointed out that if the cycle could be only slowed, while at the same time permitting normal uptake of O_2 , then CO_2 could be interpreted as "stored" although it was not produced. Available knowledge of the functionings of the Krebs cycle, however, indicate that this is less probable than the former suggestion.

Reference to the above impresses one with the possibility of CO_2 storage by reversal (or at least equilibrium shifts) in the reactions of the Krebs cycle, as well as CO_2 storage by buffering, alkaline reserve increase, excretion, or secretion.

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SUMMARY AND CONCLUSIONS

As a result of the study of the effects of inhalation of CO₂ rich air by mice, rats, dogs, and humans, the following were concluded:

(1) A fundamental difference between the response of large mammals (dogs and humans) and small mammals (mice and rats) was demonstrated, i.e., the oxygen consumption of dogs and humans was slightly increased while the oxygen consumption of mice and rats was significantly depressed.

(2) Inhalation of high CO₂ constituted a physiological "stress" for mice and rats which resulted in loss of proper temperature control as evidenced by a reduction in body temperature.

(3) The control of body temperature and metabolism was (a) established at different temperature levels, (b) lost or impaired by inhalation of CO₂ and this loss was to different degrees, and (c) demonstrated to be of such a nature that some mechanism of the animals was able to change the rate of drop of metabolism as measured by oxygen consumption. As the recognized seat of temperature control, the hypothalamus is assumed to be this mechanism.

(4) From the conditions and data of the present experiment, it appeared that a mechanism in lower mammals controlled the rate of metabolism and that as metabolism dropped, body temperature dropped as heat dissipation exceeded heat production. The hypothalamus is assumed to be this mechanism.

(5) As an easily produced and controlled "stress", pCO₂ is suggested to be of use in collection of quantitative as well as qualitative data (qualitative data is the only type of data which can be collected using most other forms of stress).

(6) Inhalation of CO_2 rich air resulted in a significant drop in the "measured" R. Q.'s to below the lowest theoretical of .707 in mice, rats, dogs, and humans indicating this to be a universal response in mammals.

(7) The above drop observed in the "measured" R. Q.'s was the result of the storage of CO_2 in the body.

(8) The blood buffers accounted for a small portion of this storage of CO_2 .

(9) Tissue buffers did not account, in mice and rats, for the stored CO_2 not accounted for by blood buffers.

(10) In addition to CO_2 buffered by the blood and tissues, other suggested avenues of "storage" are (a) shifts in equilibrium reaction which resulted in incorporation of CO_2 into members of the tricarboxylic acid cycle, (b) secretion of carbonate by the pancreas and salivary gland, (c) excretion by the skin and kidneys, (d) release of molecular CO_2 through moist skin, and (e) shift toward fat metabolism resulting in a lessened CO_2 production.

(11) That there was a shift toward fat metabolism in the animals studied was apparent from the observations: (1) of the presence of an O_2 debt represented by substances of low R. Q., and (2) the fact that more CO_2 was stored in the bodies of mice and rats than could be accounted for by blood and tissue buffers. The animals would have had an obvious advantage in such a shift from carbohydrate to fat metabolism while inhaling high CO_2 because more calories are released for fats per liter of CO_2 produced than for carbohydrates.

(12) A shift toward fat metabolism aids in an explanation of the establishing of uniform metabolic states in the subjects, i.e., regardless of the initial R. Q.'s, all subsequent R. Q.'s tended to reach a common level in a species. 170638

(13) A portion of the CO_2 "stored" during inhalation of CO_2 rich air was not recovered in expired air during a "recovery" period while inhaling atmospheric air.

(14) An oxygen debt was accumulated during inhalation of CO_2 rich air.

(15) Most of the O_2 debt was repaid during the first few minutes indicating that this portion of the debt was alactacid in nature.

(16) During this same period, expired air R. Q.'s were low indicating that the substances representing the alactacid O_2 debt were of low R. Q.

(17) In consideration of this and a possible shift toward fat metabolism during inhalation of CO_2 rich air, it is suggested that accumulated ketone bodies represented the alactacid O_2 debt.

(18) The most rapid release of the CO_2 during recovery was during the first few minutes.

(19) The persistence of high R. Q.'s during the first 10-15 minutes of recovery indicated that some of the excess CO_2 was stored elsewhere than the blood, for that stored in the blood would have been quickly given up during inhalation of atmospheric air.

(20) Under the condition of the experiment, R. Q.'s varying from .25 to 2.50 were recorded for normal subjects indicating the flexible nature of the "measured" R. Q. and the great care that must be exercised in measuring and interpreting the R. Q.

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