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A Simple Technic for Studying the Periodicity and Survival of the Respiratory Center.

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It was previously reported[1] that the isolated unperfused head of the young animal, unlike that of the adult, continues to gasp for some minutes following cessation of the cerebral blood flow and that the duration of gasping, as well as the total number of gasps, is inversely proportional to age for animals up to or slightly past the period of weaning. Thus, young rats (under 5 or 6 weeks of age) display two periods of gasping movements: an initial or aerobic series (I) of 6 to 12 gasps which lasts for a period of 15-40 seconds; and a second or anaerobic series (II) which begins 20-50 seconds after cessation of the initial series and lasts for a variable time depending upon age. This second series continues for 25-30 minutes in the newborn rat, 12-16 minutes in the 7-day-old animal, 4-7 minutes in the 14-day-old, 2-3 minutes in the 21-day-old and 1¼-1¾ minutes in the 28-day-old. Rats older than 5 or 6 weeks do not show a second series. Similar observations have been made on the ischemic heads of rabbits, cats, and dogs.[2]

Using 12-15-day-old rats (18-25 g) as test animals, it can be shown that various chemical agents administered to the animal prior to decapitation influence greatly the duration, frequency and character of gasps of either the initial or second series, or both. Chemical agents so tested are usually injected subcutaneously or intraperitoneally. In some instances they are given by mouth, or if volatile, as the general anesthetics, they are inspired. Following an interval ranging from 5 minutes to several hours or even days, depending upon the rapidity of action of the test material, the head is quickly isolated. The gasps resulting are mechanically recorded by use of a few simple pieces of physiological apparatus, such as a small burette clamp for holding the head and a light heart lever to which the mandible is attached by means of a bent pin. Action potentials of the brain stem can also be recorded readily with suitable equipment.

Since the survival time, as well as the total number of gasps, is influenced by litter or family characteristics, which in turn are modified by the state of development, the nutritive condition and the degree of hydration of the animal, it is important that the tests be carried out on litter mates subjected to identical cage conditions. Untreated litter mates of 14 days of age yield results which are remarkably uniform. Such animals show a respiratory pattern of 25-30 gasps following the onset of anoxia, there being a relatively constant number of gasps (about 8) in the initial series and a slightly variable number (17-22) in the second. The standard deviation of the mean number of gasps for this age group is slightly less than 2. In a series of preliminary experiments on 35 litters comprising 244 animals, the average variation in the survival time of untreated litter mates was found to be 8.4%; the average variation in the number of gasps of the second series was 6.1%.

The results for the test animals are compared with those of the litter mate controls given an amount of vehicle (usually 0.9% NaCl) equal to that used in the treated animals. Some drugs greatly increase the frequency and number of gasps and the duration (survival) of gasping; others diminish survival and alter the number and character of the gasps. Deviations from control values can be conveniently expressed in per cent.

With this relatively simple preparation and procedure, the following, which will be reported later in detail, can be demonstrated: (1) Survival of the respiratory center varies

[1] Selle, W. A., and Witten, T. A., PROC. SOC. EXP. BIOL. AND MED., 1941, **47**, 495.

[2] Selle, W. A., PROC. SOC. EXP. BIOL. AND MED., 1941, **48**, 417.

with blood glucose and glucose, lactate and pyruvate can counteract insulin; (2) the initial aerobic gasps are inhibited by minimal amounts of cyanide (0.1 cc of 0.01M) without alteration of the anaerobic ones; while (3) iodoacetic acid (0.1 cc of 0.01M) has the reverse action; (4) survival of the center is shortened by dinitrophenol, thyroxin, and other agents increasing metabolism; (5) gasping is depressed by most hypnotics and general anesthetics but may be stimulated by suitable doses of alcohol, morphine and chloralose; and (6) metrazol counteracts barbiturate depression.

The influence of temperature on the frequency and duration (survival) of the periodic discharges of the respiratory center can be dramatically demonstrated in 10-day-old animals (or younger) by immersing the isolated head in water of 20° and 40°C. If the area over the brain stem is quickly cooled with ethyl chloride spray, gasping is abruptly suspended; upon warming, gasping is resumed and a more or less normal series ensues. Heads of 1- to 4-day-old rats have been "revived" for a short period of activity after more than 50 minutes of cooling.

Summary. A method for studying the periodicity and survival of the primitive respiratory mechanism of young animals is described. Certain chemical and physical factors capable of influencing frequency, duration, and pattern of these periodic movements are indicated.

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Extensive Insulin Tolerance in Diabetic Dogs.*

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Soon after the introduction of insulin into clinical practice, it was observed that the amount of the new hormone required to control the glycosuria in patients with diabetes mellitus depended in part on the amount of available carbohydrate in the diet. Elaborate attempts were made to establish a quantitative relation between the insulin requirement of the patient and the amount of carbohydrate obtained as such in the food together with that which might arise through the conversion of protein and fat. Some success attended these efforts. It was soon found however that wide variations in the insulin requirement of certain patients occurred from time to time in spite of a constant diet and that enormous amounts of insulin were needed for certain patients.[1] The concept of insulin sensitivity and of insulin resistance thus arose. The precise nature of these states seems to be little understood and the present report is presented in the hope that it may contribute to the solution of this problem.

In a recent monograph, Jensen[2] states that about one unit of insulin per kilogram of body weight is required per day to maintain normal carbohydrate metabolism in the depancreatized dog. In our experience this figure is too low. Most of these animals require from 2 to 3 units per kg if good control of the glycosuria is desired. In comparison with these figures the amounts of insulin required to establish a comparable control of glycosuria in dogs with certain types of partial pancreatectomy seem surprising.

Nine male dogs, varying in weight from 8.2

* This work has been aided by grants from the Josiah Macy, Jr., Foundation, the Douglas Smith Foundation for Medical Research of The University of Chicago, and Armour and Company. The insulin used was furnished by the Eli Lilly Company.

1 Glass, W. I., Spingarn, C. L., and Pollack, H., *Arch. Int. Med.*, 1942, **70**, 221.

2 Jensen, H. F., *Insulin*, The Commonwealth Fund, New York, 1938.