metabolism depending upon the previous food intake of the animal. They may help towards a better understanding of the factors governing the metabolic pathways on different diets, and especially the many facts accumulated on the effect of fasting or fat-feeding on carbohydrate metabolism. In general, they stress the importance of ascertaining the nutritional status of the animal in carrying out enzymatic studies.

A detailed report will appear elsewhere. We wish to express our appreciation to Prof. E. Lundsgaard for his interest and helpful counsel in conducting these experiments.

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A Simple Method for Direct Comparison of the Depressant Effect of the Barbiturates on the Respiration and Circulation

IN 1926, Knaffl-Lenz[1] introduced a method for the bioassay of digitalis preparations by determining the minimal lethal dose on intravenous injection in anæsthetized guinea pigs. The method, which may be used for all kinds of cardiac glucosides, has since become official in, for example, Britain[2] and Sweden[3]. According to this procedure, the solution to be tested is introduced into the vena jugularis under constant pressure and at constant speed (either from a burette with a Mariotte stopper or with a motor-driven injection apparatus). The lethal dose is determined by direct observation of the cardiac standstill (concerning the details of the procedure, see, for example, Burn[4], Fønss Bech[5] and Goldberg[6]). The number of animals required is determined by the degree of accuracy one wishes to give the results; this may be calculated with the help of the usual statistical methods.

A similar method can also be used for comparison of the depressant effect of the barbiturates on the respiration and circulation. The guinea pigs in this case are anæsthetized with urethane. The dose required to produce cessation of the respiration may be ascertained by direct observation, although a self-registering device is, of course, also possible. When respiration ceases, the dose and time are noted, the thorax is opened and artificial respiration by a previously prepared connexion between the trachea and a Sterling pump is started. The cessation of cardiac activity is observed as in the Knaffl-Lenz method, and the dose and time required are noted. The doses required for the cessation of respiration and cardiac activity are thus determined on one and the same animal. The concentration of barbiturate, which must be in solution in the form of an alkali salt, is such that the dose required for the cessation of cardiac activity will be about 1 ml. per 100 gm. body-weight. The suitable rate of injection will then be approximately 0·5 ml. per min.

Doses required to produce cessation of respiration and circulation in guinea pigs after intravenous injection of some common barbiturates

Barbiturate	Concentration (per cent)	No. of animals	Dose for respiratory standstill (*R*) (ml./100 gm. body-weight)	Dose for cardiac standstill (*C*) (ml./100 gm. body-wt.)	*R*/*C* (as percentage)
Sodium 5-*iso*-amyl-5-ethyl-barbiturate ('Amytal sodium')	2·75	17	0·18±0·019	0·75±0·019	24
Sodium *N*-methyl-cyclo-hexenylmethyl barbiturate ('Evipal sodium')	2·2	7	0·055±0·015	0·98±0·039	6
Sodium *iso*propyl-β-brom-allyl-*N*-methyl-barbiturate ('Narkotal')	2·2	14	0·055±0·0042	0·72±0·030	8
Sodium 5-ethyl-5-(1-methyl-butyl)-thio-barbiturate ('Pentothal sodium')	1·2	9	0·058±0·0057	1·02±0·048	6

A simple method for such comparisons is of great practical value, since it has proved that the depressant effect of the barbiturates on the respiration has shown a tendency to increase if their duration of action is diminished.

In the accompanying table are given the results of a number of experiments using the method described. 'Amytal', with its moderate duration, has been compared with intravenous anæsthetics of ultra-short duration, such as 'Evipal', 'Narkotal' and 'Pentothal'. The depressant effect on the respiration of the last three preparations when injected intravenously is, as seen from the table, both absolutely and relatively in a totally different class from that of 'Amytal'. The dose required for cessation of circulation is in the case of 'Amytal' about four times as great as the dose inhibiting the respiration, while the corresponding value for the three other compounds is about fifteen times.

The importance of artificial respiration after cessation of spontaneous respiration under intravenous barbiturate anæsthesia is demonstrated, in short, in an extremely striking way. The margin between cessation of respiration and cardiac activity respectively brought about by compounds of the 'Amytal'-type is not as favourable for a successful treatment with artificial respiration, although this is far from insignificant. For these preparations, which are chiefly used in ambulant practice and are administered by mouth, the considerably smaller absolute toxicity on the respiratory centre is of all the greater importance. It is, of course, as a matter of fact, this form of toxic effect which determines the practical usability of the ordinary hypnotics.

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