cate that the decreased tolerance to histamine of the adrenalectomized mouse is directly related to the increase of hemoconcentration caused by the drug. It appears that the angiotoxic effect of histamine is potentiated by the removal of the adrenals. But, as the animals are protected with cortisone and adrenaline, they show a lower degree of hemoconcentration when injected with histamine. It seems that these hormones protect the animals by increasing the resistance of the vascular bed to the toxic effect of histamine on small vessels. This interpretation is consistent with the results obtained either with adrenaline alone, or with the anti-histaminic drugs, which, as it is admitted by certain authors(10), have a definite effect on the small vessels. The fact that neither cortisone nor cortisone and adrenaline afford any protection to the normal mice is consistent with the results obtained with promethazine. In the normal mouse, the toxicity of histamine may be due to a different mechanism.

Summary. (1) When injected into adrenalectomized mice, cortisone enables these animals to tolerate 5 doses of histamine, which are usually lethal for the adrenalectomized animals. (2) Under the same conditions, adrenaline enables adrenalectomized mice to tolerate 5 to 10 lethal doses of histamine. When, however, adrenalectomized mice are treated with both cortisone and adrenaline, they are able to tolerate 50 to 100 lethal doses of histamine, and their resistance to the drug is brought back to the normal level. (3) The relationship between increased tolerance to histamine and lowering of the hemoconcentration effect of histamine caused by cortisone and adrenaline in adrenalectomized mice suggests that these hormones exert their protective effect against the angiotoxic action of histamine on the small vessels. (4) Contrasting with this remarkable action of cortisone and adrenaline in adrenalectomized mice, these hormones do not modify the toxicity of histamine in normal animals.

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Choline Oxidase Activity in Young Rats.* (19265)

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The low activity of choline oxidase in several rat liver tumors(1-3) as compared with normal rat liver, made it of interest to study the activity of this enzyme in the livers of young rats. The succinoxidase system, which is chiefly associated with the large granule (mitochondrial) fraction of rat liver, had been shown earlier(4) to increase rapidly from low levels in newborn rats to the normal adult level in 12-15 days. As choline oxidase has also been shown to be largely associated with the large granule fraction of rat liver(5), in the present study both succinoxidase and choline oxidase activity were measured. The results obtained with succinoxidase are in agreement with the earlier study(4). Choline

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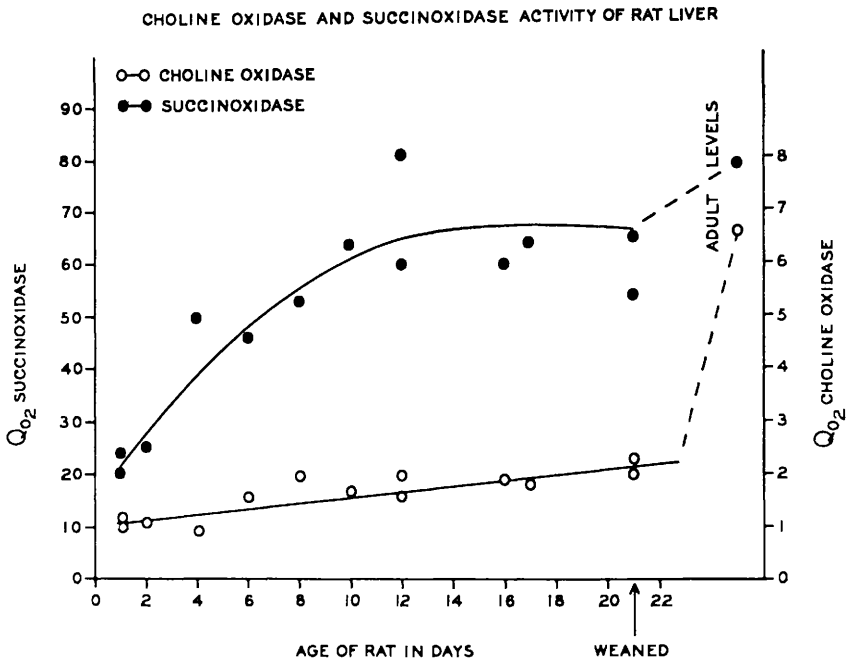

FIG. 1. Choline oxidase and succinoxidase activity of rat liver in unweaned rats.

oxidase activity was found to be low at birth, and at the time of weaning (ca 21 days) attained only one-third of the activity of normal adult rat liver.

Methods. Rats of the Wistar strain, inbred in our laboratories for seven years, have been employed in these studies. The colony is maintained on a Dog Chow ration. The young rats were weaned at 20-22 days of age, usually 21 days. The liver of the rats was assayed for succinoxidase and choline oxidase activity at varying periods after birth. Succinoxidase activity was measured manometrically(6) with the exception that Al Cl_3 was not added. Choline oxidase was measured manometrically as described previously(5). The Q values were calculated in all cases using the assumption that the dry weight of rat livers represents 30% of the wet weight. A few measurements, under similar conditions, of the choline oxidase activity of rat kidney cortex, were also made.

Results. The data obtained on the choline oxidase and succinoxidase activity of the livers of rats from one to 21 days of age are summarized in Fig. 1. Each point represents the value obtained on pooled livers from two to eight animals. The succinoxidase activity, in agreement with Potter, Schneider and Liebl (4), increased rapidly and values in the normal range were obtained by 10-12 days after birth. However, with our animals, the average succinoxidase activity of 32 rats from 10-27 days of age was 20% lower than the adult average. As is shown, choline oxidase activity increased at a much slower rate, attaining at weaning approximately one-third of the adult level. The adult levels represent the values obtained on 27 rats weighing between 200 and 400 g and are shown in Fig. 1.

Choline oxidase activity in the normal adult range was observed when the rats attained approximately 40 days of age, although there was considerable variation among different litters. Small animals were observed to have lower activity than large animals from litters of the same age. The choline oxidase activity of the livers of 95 weaned rats was measured as a function of their age and body weight. The data illustrating the relationship between activity and body weight are plotted in Fig. 2. Each point, except where indicated, represents a single rat. The values on the pre-weanling rats, for which weight as well as age had been

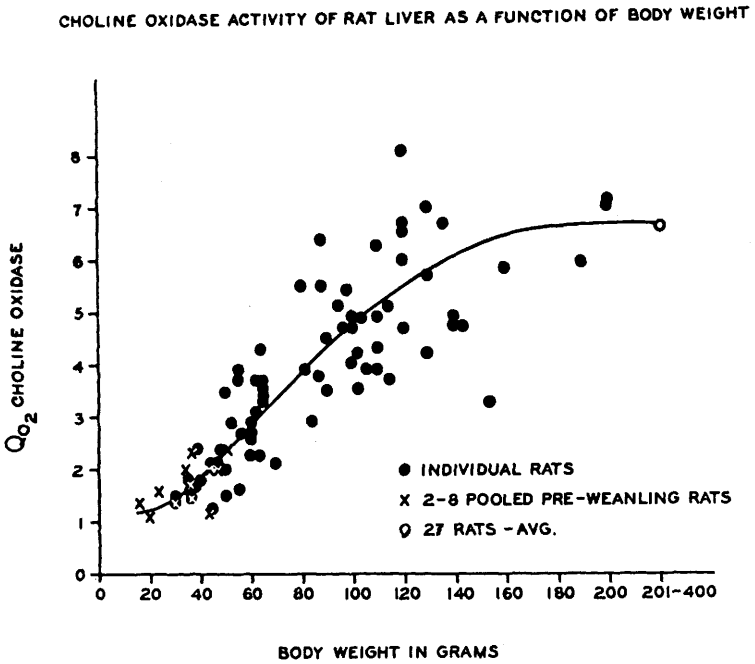

FIG. 2. Relationship of choline oxidase activity of rat liver to body wt.

recorded, are also included for comparison. It can be seen that the activity of choline oxidase in rat liver increases as a function of the body weight reaching maximal values when the animals weighed 120-150 g.

The choline oxidase activity of rat kidney cortex has also been measured in several animals. In adult animals this tissue ($Q = 3.5$) yields approximately one-half as much activity as liver. The activity of the kidney cortex from 8-day-old rats (weight 23 g) was one-seventh of this ($Q = 0.5$) while the tissue in 22- and 23-day-old rats (weight 45-56 g) was one-third ($Q = 1.1$) of the adult value.

Discussion. Although both succinoxidase and choline oxidase activity are associated with the large granule (mitochondrial) fraction of rat liver, the data presented indicate that these two enzymes increase in activity in the livers of young rats at widely different rates, choline oxidase activity increasing much more slowly. The choline oxidase activity of rat kidney cortex has also been observed to be low in newborn rats and to be low at weaning. Presumably the diet used was adequate in all nutritional factors, however, the possibility that the slow rate of increase in choline oxidase activity may be due to a limiting nutritional factor, is under investigation.

The slow increase in choline oxidase activity in young rats may be related to the high requirement for choline or preformed methyl groups by the weanling rat, although a low level of choline oxidase activity would be expected to preserve for other purposes such choline as was available to the animal. The apparent necessity for choline to be oxidized to betaine(7,8) in the rat before its available methyl group can be utilized in transmethylation reactions, suggests the need for data on the activity of other enzymes concerned with labile methyl synthesis and utilization in weanling rats before the significance of low choline oxidase activity may be properly evaluated. Preliminary experiments indicate that dimethylthetin-homocysteine and betaine-homocysteine transmethylase activity do not parallel choline oxidase activity.

Summary. (1) Choline oxidase activity is low in the livers of newborn rats and increases to only one-third of the adult level by weaning, in contrast to the rapid attainment of adult levels of succinoxidase activity. (2) Choline oxidase activity is low in the kidney

cortex of newborn rats and also rises to adult levels very slowly. (3) The slow increase in the choline oxidase activity of rat liver as a function of the weight of the animal is demonstrated.

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Surgical Anesthesia in Rabbit and Dog with Intravenous Amphenone B.* (19266)

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We have previously reported that Amphenone "B"(1) has a potent depressant action on the central nervous system of the rat (2). We now report the experimental use of intravenously administered aqueous solutions of this compound to induce complete surgical anesthesia in the rabbit and dog.

Female New Zealand White rabbits and small female mongrel dogs were maintained on a stock diet. Food was removed the evening preceding operation. No preoperative medication was employed. Either a 2% or 4% aqueous solution of Amphenone "B" was employed. All injections were given by intermittent intravenous infusion beginning with a sufficient volume to induce prompt anesthesia. The surgical procedures listed in Table I were immediately performed. Supplemental doses of drug were administered intravenously as required for maintenance of surgical anesthesia.

The behavior of these animals during the course of these observations warrants the conclusion that Amphenone "B" possesses a sufficiently profound depressant action on the central nervous system to abolish pain response in the rabbit and dog. The accompanying respiratory depression is sufficiently limited to afford a substantial margin of safety in the performance of major surgical procedures. Complete relaxation of the abdominal muscles was noted during each operation. Visceral manipulation such as traction on the uterus and exterioration of the bladder and intestines was carried out with ease and without significant effect on respiration or on the depth of anesthesia. The blood retained a normal oxygenated appearance and only the expected amount of blood loss was observed.

The rate of recovery was recorded as the length of time required for each animal to spontaneously assume an upright position. The speed with which such recovery occurred suggests that the compound is rapidly cleared from the blood.

In the rat Amphenone "B" effects a marked enlargement of the thyroid and adrenal and exerts an atypical folliculoid action on the female genital tract(3-5). In the rabbit it exhibits a weak progestational action on the uterus(4). A number of steroid compounds, notably progesterone, have anesthetic properties when administered in high dosage either intraperitoneally or intravenously(6). Accordingly, the association of anesthetic and endocrine effects in a non-steroid compound such as Amphenone "B" presents a striking parallel to the biological phenomena observed with steroids.

Summary. Intravenously administered Amphenone "B" produces surgical anesthesia in the rabbit and dog. The margin of safety is

* 1,2 bis-(p-aminophenyl)-2-methylpropanone-1 dihydrochloride.

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