Summary. Homoplastic suprarenal cortices may incorporate and persist for as long as 5 months in the eyes of normal hosts. The extent of cortical regeneration in suprarenal grafts as well as the frequency of persistence is augmented by suprarenalectomy and by homopituitary implantation. The evidence seems to indicate that differentiation in cortical transplants is conditioned by the cortico-adrenotropic principle of the anterior hypophysis. The medullary tissue is relatively specialized but it may persist in homoplastic grafts if the period of nutritional interruption is minimized.

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Effect of Beta-methylcholine-urethane on Normal and on Reflexly Inhibited Intestine.*

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Although acetylcholine produces marked stimulation of the isolated intestine,[1] it is not suitable for increasing the motility of the intestine *in situ* because of its rapid hydrolysis by the cholinesterase of the blood,[2] its severe blood-pressure lowering effect, and its indiscriminate stimulation of autonomic ganglia (nicotinic action). Protecting acetylcholine from hydrolysis by the use of physostigmine potentiates and prolongs the intestinal effects of acetylcholine[3] but the other two objections are still applicable. Acetyl-beta-methylcholine lacks the nicotinic action[4] and is somewhat more stable in blood, but it also has severe blood pressure effects due to cardiac slowing especially when given parenterally.[5] A sharp fall in blood pressure causes reflex production of adrenine and sympathin, both of which are inhibitors of the intestine. These compensatory responses occur

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1 Dale, H. H., *J. Pharm. and Exp. Therap.*, 1914, **6**, 147.

2 Matthes, *J. Physiol.*, 1930, **70**, 338.

3 Zimmerman, L. M., Frank, R., and Necheles, H., *Arch. Surgery*, 1936, **33**, 187.

4 Simonart et Simonart, *Arch. internat. de Pharm. et de Therap.*, 1935, **51**, 76.

5 Starr, I., *Trans. Assn. Am. Physicians*, 1936, **51**, 326.

following injection of blood-pressure lowering choline derivatives.[6] The carbamic esters of choline and of beta-methylcholine which are called carbaminoylcholine and beta-methylcholine-urethane (carbaminoyl-beta-methylcholine) are comparatively stable in blood and the latter has the additional advantage of lacking the nicotinic action.[4] Carbaminoyl choline was given by Bosse[7] to patients having atonic bladders and intestines. In 12 patients with mechanical ileus treated with carbaminoyl choline he found increased peristalsis, indicated by borborygmi followed by the passage of flatus and stools. However, the compound has some undesirable side actions and possesses the nicotinic action. Simonart has concluded that, other properties being equal, a choline compound free from the nicotinic action should be preferable for clinical application, and the major effect of introducing the beta-methyl group is to eliminate the nicotinic action. Starr[5] used beta-methylcholine-urethane on several patients with postoperative abdominal distention and reported favorable results. He stated that when given in ascending doses the first painful effects were cramps and urethral spasm without significant effect on blood pressure. Molitor[8] found the compound to produce defecation in unanesthetized dogs. Farber[9] found that a small intravenous dose causes a fall in blood pressure due to vasodilatation, but the dose must be quite large before heart slowing is produced. These facts suggest that beta-methylcholine-urethane (b-m-c-u) lacks the characteristics which make acetylcholine and many other choline derivatives unsuitable for use in increasing the tonus and activity of the intestine. We have studied the effects of b-m-c-u on the motility of the normal and of the reflexly inhibited intestine of unanesthetized dogs.

Intestinal activity was recorded from jejunal segments in the form of Thiry fistulæ. A balloon inserted into the fistula was connected by means of rubber tubing to one arm of a mercury manometer, the other arm of which floated a writing point. Two such systems were used to record simultaneously the activity of innervated and of denervated Thiry fistulæ in the same animal. Four dogs were used for recording effects on intestinal motility. Each of 3 of these dogs had 2 Thiry fistulæ, one of which was innervated and the other denervated by cutting the mesentery and stripping the nerve fibres from the blood vessels. The fourth dog had a single

[6] Hermann, H., Jourdan, F., Morin, G., and Vial, J., *Arch. internat. de Pharm. et de Therap.*, 1937, **57**, 403.

[7] Bosse, U., *Klin. Wochensch.*, 1937, **16**, 1365.

[8] Molitor, H., *J. Pharm. and Exp. Therap.*, 1936, **58**, 337.

[9] Farber, S., *Arch. internat. de Pharm. et de Therap.*, 1936, **53**, 377.

Thiry fistula which was denervated by removal of the coeliac ganglia and vagotomy above the diaphragm. Rectal stimulation was done by inserting a catheter into the anal canal past the sphincter and moving the catheter back and forth to cause sphincter activity. Direct blood pressure records were taken from the femoral arteries of doubly-vagotomized dogs under ether-morphine anesthesia. Beta-methyl-choline-urethane $(CH_3)_3NClCH_2CH\ CH_3\ OCONH_2$† was given subcutaneously or intravenously.

Effect of b-m-c-u on intestinal motility: In the 4 animals after subcutaneous injections of 0.1 mg/kilo of b-m-c-u the tonus and the amplitude of rhythmic contractions were increased in both the innervated and the denervated intestinal segments. No definite effect was observable when the subcutaneous injection was 0.07 mg/kilo or less. This is about 50% larger than the dose which Starr[5] used. Following subcutaneous injections the initial effects occurred within 3 to 6 minutes and became maximal within 15 minutes. Effects were observable as long as 45 minutes following the injection.

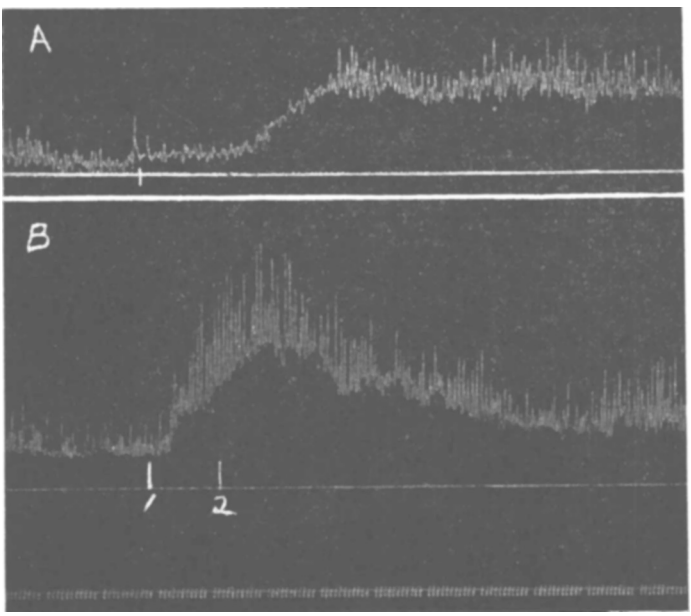

FIG. 1.

Effect of beta-methylcholine-urethane on intestinal tonus and motility. Both A and B are balloon mercury manometer records of motility of the same Thiry fistula on different days. In A, 0.15 mg/kilo of b-m-c-u was given subcutaneously. In B, 0.05 mg/kilo was given intravenously between 1 and 2. Time in 5 seconds and 1 minute intervals.

† Supplied by Merck & Co., Rahway, N. J.

An intravenous dose of 0.05 mg kilo of body weight injected within an average period of 75 seconds produced an increase in tonus of from 9 to 24 mm of Hg and an increase in the amplitude of rhythmic contractions in each of 6 cases. The tonus increase began within one minute after beginning the injection and lasted from 9 to 15 minutes. Fig. 1 shows a typical response to a subcutaneous (A) and an intravenous (B) injection in the same animal.

The fact that the innervated and the denervated intestine showed the same type of response to the drug suggests that its action is peripheral.

Within a few minutes after subcutaneous injection of 1.0 mg of

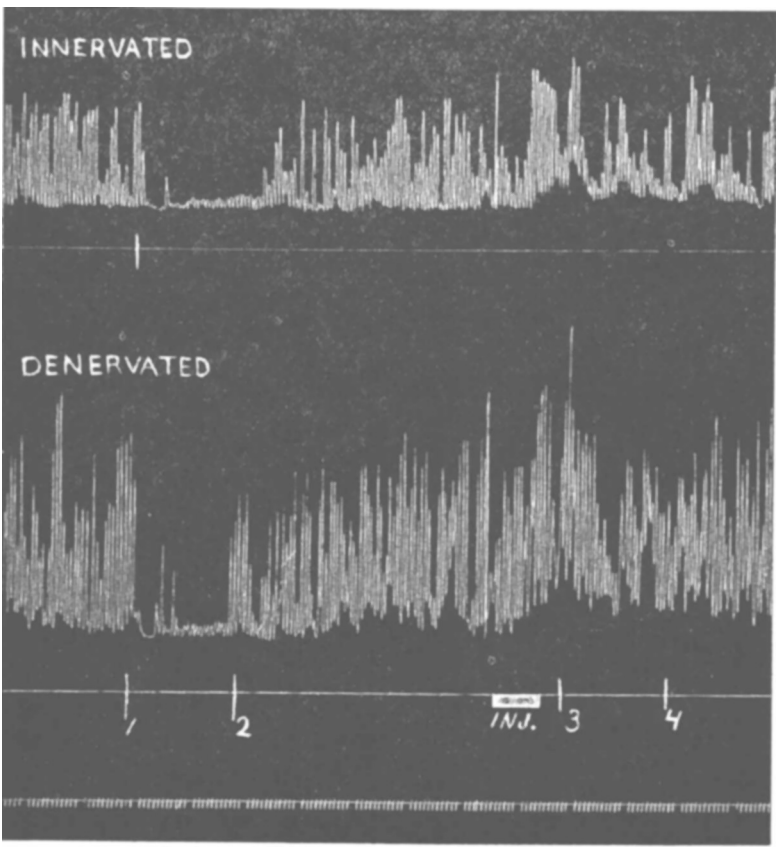

FIG. 2.

Prevention by beta-methyl-choline-urethane of reflex inhibition of intestinal motility. Balloon-mercury-manometer records of activity of innervated and denervated Thiry fistulæ. Rectal stimulation between 1 and 2, also between 3 and 4. Injection at INJ (intravenously) of .04 mg/kilo of b-m-c-u. Time in 5 seconds and 1 minute intervals.

atropine neither the subcutaneous nor the intravenous administration of the above doses of b-m-c-u produced any effect on intestinal motility.

Rectal stimulation causes reflex inhibition of the tonus and rhythmic contractions of the intestine. The reflex inhibition thus produced utilizes sympathetic nerves, the activation of which results in the entrance of sympathin into circulation so that a denervated intestinal segment is inhibited during rectal stimulation.[10] It has been indicated that sympathetic nerves are utilized in reflex paralytic ileus.[11] B-m-c-u when given intravenously, completely opposed the inhibitory effects of rectal stimulation on both the innervated and the denervated intestine. Fig. 2 shows a typical record. Intestine-inhibiting effects of rectal stimulation were only partly prevented by the relatively small subcutaneous doses given. These facts support the opinion that b-m-c-u might be useful in opposing reflex paralysis of the intestine.

Results of subcutaneous injections of b-m-c-u into 8 stock dogs (dosage 0.10 to 0.30 mg/kilo) were similar to those reported by Molitor.[8]

Blood-pressure effects of intestine-stimulating doses of b-m-c-u: In experiments on 8 vagotomized dogs under ether-morphine anesthesia the following facts were observed. 1. Subcutaneous doses ranging from the same to 40% greater than the doses used in the studies on intestinal activity had no effect on mean arterial blood pressure. 2. Intravenous doses ranging from 0.007 to 0.15 mg/kilo/min produced marked but transitory decreases in blood pressure, but without decreasing the heart rate. 3. When an intravenous injection was maintained at a constant rate for a period of 10 minutes, recovery from the initial drop in pressure occurred. For example, in one case using a dose of 0.007 mg/kilo/min the blood pressure dropped from 128 to 102 mm/Hg within 15 seconds, then after one minute the pressure rose to 118 mm/Hg and was maintained at that level until the end of the injection. If the blood pressure changes appearing in these acute experiments are indicative of what occurs in the unanesthetized animal, a subcutaneous dose of b-m-c-u sufficient to cause increased tonus of the intestine is without blood pressure effects.

Summary. Beta-methylcholine-urethane, a drug which has been reported to have beneficial effects in cases of postoperative abdominal distention, causes a marked increase in the tonus and the amplitude

[10] Youmans, W. B., and Meek, W. J., *Am. J. Physiol.*, 1937, **120**, 750.

[11] Markowitz, J., and Campbell, W. R., *Am. J. Physiol.*, 1927, **81**, 101.

of rhythmic contractions of innervated or of denervated jejunal segments of unmedicated dogs. The drug opposes inhibition of the intestine by reflexly activated sympathetic nerves or inhibition by the sympathin released as a result of the activity of these nerves. The effects of the drug on intestinal motility are prevented by atropinization.

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Effect of Anol and Dihydrotheelin on Mammogenic Activity of Pituitary Gland of Rabbits.*

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It has been shown that estrogen stimulates the production of a mammogenic hormone entity by the anterior pituitary which is directly responsible for the growth of the mammary gland.[1, 2] More recently, Gomez and Turner[3] reported that anol stimulated the growth of the mammary glands of ovariectomized rabbits, rats and male mice and suggested that like estrogen, the action of anol upon the mammary gland is probably indirect by way of the pituitary gland. It is interesting, therefore, to determine the effect of various estrogens and chemical substances having the dual activity of estrogenesis and carcinogenesis upon the mammogenic activity of the anterior pituitary gland. In the present communication, the effect of anol and dihydrotheelin is reported.

A group of 8 young adult virgin female rabbits were each given by subcutaneous injection once daily 0.1 mg of anol‡ for 25 days:

* Aided in part by a grant from the International Cancer Research Foundation.

† Contribution from the Department of Dairy Husbandry, Missouri Agricultural Experiment Station, Journal Series No. 577.

1 Gomez, E. T., Turner, C. W., and Reece, R. P., PROC. SOC. EXP. BIOL. AND MED., 1937, **36**, 286.

2 Gomez, E. T., and Turner, C. W., *Mo. Agr. Exp. Sta. Res. Bul.*, 1937, 259; PROC. SOC. EXP. BIOL. AND MED., 1938, **37**, 607.

3 Gomez, E. T., and Turner, C. W., 1938, in press.

‡ The anol used in this study was prepared by the British Drug Houses, Ltd., London. This anol contains 10 rat units of estrogenic activity per milligram of the crystalline material.