taken and animal killed by the intravenous injection of air. Tissue samples were removed as rapidly as possible and prepared immediately for analysis. Each sample of tissue was weighed; ground in a Waring blendor to form a coarse suspension and finally ground with a Ten Broeck tissue grinder until each sample could be handled with a tuberculin syringe. In order to facilitate grinding each sample of tissue was mixed with an equal volume of saline, except for muscle with which 2 volumes of saline were used for each volume of tissue. Preliminary experiments indicated that added myanesin could be recovered satisfactorily from such tissue mashes. However, it was not possible to analyze for "total" myanesin since tissue-reagent blanks were excessively high.

The results of all experiments are summarized in Fig. 4 in which ratios of tissue/plasma concentration are plotted against plasma concentration. As predicted it is obvious that myanesin is widely distributed, and approximately according to water content of each tissue. A notable exception to this, however, is seen in the case of brain in which the ratio of tissue/plasma was always more than unity and average approximately 2. The explanation for this finding is at present obscure, but of considerable interest since the outstanding actions of myanesin are on the central nervous system. Since spinal fluid and saliva concentration were consistently lower than plasma, one wonders if perhaps distribution of myanesin may not in part be conditioned by lipoid solubility as well as water solubility.

Discussion. The above experiments furnish concrete evidence that the brief action of myanesin is due primarily to rapid metabolic alteration. Since myanesin has been suggested for use in a number of chronic diseases[5,6] where prolonged action is desirable, it is important that more data concerning the characteristics of the processes involved in the alteration of the free drug should be obtained. Such information may furnish important leads as to means whereby longer acting drugs may be synthesized.

Summary. 1. From a study of plasma concentrations of animals infused continuously, it has been shown that dogs can dispose of between 1 and 2 mg of myanesin per kg per minute, irrespective of plasma concentration between the limits of 50 and 130 μg per ml. 2. The rapid disposition of myanesin is due primarily to metabolic alteration. 3. Myanesin is widely distributed in the body approximately according to water content. A notable exception to this is found in the brain where tissue/plasma ratios of greater than 2 are observed.

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Effect of Cycloheptenylethyl Barbituric Acid, "Medomin," on Intestinal and Uterine Smooth Muscle.*

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The following investigation was undertaken to determine the effect of cycloheptenylethyl barbituric acid "Medomin" on intestinal and uterine smooth muscle and the effects of a number of short and ultra-short barbiturates on the intact intestine of the non-anesthetized dog.

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Methods. Excised Intestine. Excised longi-

tudinal segments of rabbit intestine were used. The animals were killed by cerebral concussion and exsanguination. Some of the tissues were used immediately after being removed while others were kept in a refrigerator in Locke's solution until needed.

One end of the muscle was fastened to an L-shaped glass rod and the other end to a muscle lever by means of ligatures. The muscles thus suspended, together with the L-shaped glass rod, were placed in a pyrex glass cylinder containing freshly made Tyrode's solution with a pH of 7.8. Two muscle segments, one of the duodenum and one of the ileum, were suspended in the same bath. The temperature of the bath was maintained at 38.5°C ± 0.2°C.

Cycloheptenylethyl barbituric acid, phenobarbital sodium and seconal sodium were used in this investigation. The drugs were weighed and placed in volumetric flasks and Tyrode's solution added to volume. In the case of cycloheptenylethyl barbiturate a solution of sodium hydroxide was added to form the soluble sodium salt before the addition of Tyrode's solution. A given amount of these solutions was added to the bath to make dilutions ranging from M/20,000 to M/1,000.

Intact Intestine. Trained non-anesthetized dogs with Thiry-Vella loops of the small intestine were used in studying the effects of this and a number of barbiturates on the intact intestine. The method of preparation of the animals was the same as that previously described by one of us.[1] The changes in the general tonus and in the rhythmical contractions were recorded by means of a rubber balloon placed within the lumen of the gut.[1] The balloon was connected to a modified Brodie bellows. The pressure within the balloon was 15 cm of water. After a normal control record had been secured the drug was injected intravenously.

Excised Uterus. Uterine segments taken from rabbits and cats were used for this research. The method of preparation of the segments was like that described for excised intestine. The same apparatus was employed for maintaining a constant temperature of the bath, for oxygenating and for recording the contractions of the uterus. Locke's solution having a pH 7.6 was used as the bath. Two segments, one from each horn of the uterus was always used simultaneously and suspended in a manner similar to that employed in studying excised segments of intestine. The drugs were weighed and dissolved in Locke's solution just preceding the experiment. A given amount of this solution was added to the bath to make dilutions of M/15,000 to M/1,000.

Intact Uterus. The method employed in investigating the intact uterus of rabbit, cat or dog was similar to that used by Barbour.[2] The animal was anesthetized with ether by inhalation. A cannula was placed in the trachea and the ether continued. Artificial respiration was used to rule out the possible effect of anoxia, in case the respiratory center was excessively depressed by the barbiturate. The uterine horns were exposed by a midline abdominal incision. A glass tube, such as described by Barbour,[2] was passed into the abdomen over the uterus through the wound and the abdominal muscles and skin securely fastened around the tube making the joint water tight. The glass tube was kept partly filled with warm Ringer's solution. The uterine horns with their circulation and nerve supply intact were brought up into the glass tube and by means of linen threads fastened to muscle levers, which wrote on smoked paper on a kymograph drum.

Results. Excised Intestine. Twenty-eight, 26 and 30 experiments were performed with cycloheptenylethyl barbiturate, seconal sodium and phenobarbital sodium respectively upon 10 pairs of excised segments of rabbit intestine. A decrease in the general tonus and in the height of the rhythmical contractions were recorded in every instance. A comparison of the results of the 3 barbiturates used in these experiments revealed the fact

[1] Gruber, C. M., Ellis, F. W., and Freedman, G., *J. Pharm. and Exp. Therap.*, 1944, **81**, 261; Gruber, C. M., *et al.*, *ibid.*, 1931, **42**, 27; Gruber, C. M., and Brundage, J. T., *ibid.*, 1935, **53**, 120; Gruber, C. M., *ibid.*, 1936, **56**, 432.

[2] Barbour, H. G., *J. Pharm. and Exp. Therap.*, 1915, **7**, 547.

that seconal is approximately twice as depressant as cycloheptenylethyl barbiturate, which in turn is twice as active as phenobarbital on the excised intestine.

Intact Intestine. Nineteen dogs with Thiry-Vella loops were used. Thiopental sodium (pentothal) (15, 20, 25 mg/kg) was injected 34 times in 14 animals; pentobarbital sodium (20 and 25 mg/kg) 6 times in 6 animals; thioethamyl (10, 20, 30 and 40 mg/kg) 14 times in 13 animals; hexobarbital soluble (evipal sodium) (25 and 40 mg/kg) 7 times in 7 animals; amytal sodium (15 mg/kg) twice in 2 animals; seconal sodium (15 mg/kg) twice in 2 animals, and cycloheptenylethyl barbiturate (10 to 25 mg/kg) 14 times in 4 animals. In every instance a sudden decrease in the general tonus was noted. In only 3 out of 79 injections of these barbiturates were we able to see a possible increase in the general tonus of the intact gut following the primary depression. In 48 of the experiments while these trained animals were recovering from the hypnosis of the drug they became so excited that the experiments had to be interrupted. Our results on these 19 animals following 79 injections of short and intermediate acting barbiturates fail to support Burnstein's[3] findings that the relaxation of the gut is followed in "every instance"—"by a gradual rise in the general tonus to above normal and increased rhythmic intestinal contractions which were maintained until the animal awakened." Our results are, however, in accord with those of Oettel,[4] who reports excitement to such extent in the animal coming out of the barbiturate (evipan and pernocton) hypnosis that the experiments had to be discontinued.

Cycloheptenylethyl barbiturate, like other barbiturates, causes a decrease in the general tonus and in the height of the rhythmical contraction of the intact gut in the unanesthetized dog. Both contractions and tonus returning to the control level in 30 to 60 minutes after the injection.

Excised Uterus. Fourteen experiments were performed on 10 pairs of segments of excised rabbit uterus and one experiment on a cat uterus. In all of these a prompt decrease in the general tonus and in the height of the contractions was observed. In a few segments the rate of the rhythmical contractions was increased by the drug.

Intact Uterus. Eleven experiments were performed on 7 rabbits, 21 experiments on 9 cats, and 2 experiments on 1 dog with the use of cycloheptenylethyl barbiturate. In cats pentobarbital sodium and seconal sodium were injected intravenously 4 and 6 times respectively. In the rabbit and dog, only a decrease in the general tonus and in the height of the rhythmical contractions were noted. In the cats, however, an increase in the general tonus was observed following 8 of the 21 intravenous injections of cycloheptenylethyl barbiturate, in 2 of the 4 injections of pentobarbital sodium and in 1 of the 6 injections of seconal sodium.

Summary. 1. Cycloheptenylethyl barbituric acid produces relaxation of the excised segments of intestine and uterus of cats and rabbits. 2. The intact intestine of dogs and the intact uterus of rabbits and dogs respond to the drug by a decrease in the tonus and a lessening of the rhythmic contractions. In the cats, however, increased tonus of the uterus was observed on some occasions. 3. In only 3 out of 79 injections of ultra-short, short and intermediate acting barbiturates was there a suggestion of an increase in the general tonus of the intact gut following the primary depression. About 50% of our experiments had to be discontinued during the period of intestinal relaxation because of the excitement produced in the animal as it was recovering from the barbiturate hypnosis.

[3] Burnstein, C. L., PROC. SOC. EXP. BIOL. AND MED., 1939, **40**, 122.

[4] Oettel, H., *Arch. f. Exp. Path. u. Pharmakol.*, 1935, **177**, 323.