

52.2 to 66.7% of that fed. On the following day the recovery was higher varying from 60.1 to 82.7%. The animals fed the β,γ -dideutero acid excreted in all cases slightly higher proportions than did those which received the α,β compound.

The analyses of the silver salts of betahydroxybutyrate showed a sufficient purity that it would be impossible for the deuterium present to be in the form of a contaminant.

The analysis for deuterium indicates that in the case of the rats fed α,β -deuterocaproate an average of 6.43% of the betahydroxybutyric acid excreted contained deuterium (calculated on the basis of one atom to a molecule of acid). Those receiving the β,γ -caproate excreted a hydroxy acid which averaged 10.89% of the deuterio-containing acid.

If the betahydroxybutyrate had originated from the α,β -deuterocaproate solely by beta oxidation, then no deuterium would be present because the β carbon atom containing the deuterium would be replaced by a carboxyl group. The retention of deuterium which did occur can best be explained on the basis of a delta oxidation. On the other hand the higher deuterium content occurring after feeding the β,γ -deuterocaproate would also seem to indicate that delta oxidation had played a part. Inasmuch as the deuterium is retained to a greater extent when on the γ carbon than on the α carbon atom in betahydroxybutyrate,¹ the higher retention here can be explained as partly traceable to delta oxidation with a consequent retention of the deuterium on the γ position. These experiments would seem to indicate the probability that delta oxidation plays an important role in the oxidation of caproic acid.

11594

Reaction of Dog's Colon to Subcutaneous Injections of Morphine.

R. D. TEMPLETON, E. A. GALAPEAUX, AND H. F. ADLER

From the Departments of Physiology, Loyola University School of Medicine, and the University of Chicago.

An increase in intestinal tone following the administration of morphine seems to be the most consistent result reported by various investigators. According to Plant and Miller¹ the most pronounced and lasting effect of morphine upon the colon of unanesthetized

¹ Plant, O. H., and Miller, G. H., *J. Pharm. and Exp. Therap.*, 1927, **32**, 437.

dogs and men is an increase in the muscular tone. Gruber, Greene, Drayer and Crawford² observed an increase in the tone of Thiery-Vella fistulae of dogs following the intravenous injection of morphine. These observations were confirmed by Krueger,³ Gruber and Brundage,⁴ Forster⁵ and others. On the other hand, a few investigators have reported a decrease in intestinal tone following morphine administration. Gruber and Robinson⁶ observed that repeated injections of morphine led to a general decrease in the tonus of the intestine. Krueger, Howes and Gay⁷ have reported that small doses of morphine are followed by a decrease in intestinal tone while large doses caused an increase.

Reports on the effect of morphine on intestinal activity have been reasonably consistent when dosage is taken into consideration. Plant and Miller¹ reported that peristaltic activity of the colon is increased by largely eliminating the periods of quiet while the time occupied in the passage of an individual wave was not materially changed. They also observed that the amplitude of peristaltic contractions varied inversely with the increase in tone. Krueger³ reported a decrease in rhythmic frequency and an increase in peristalsis and tone. The number of peristaltic waves obtained after morphine, according to Krueger, Howes and Gay⁷ increases with increasing doses and reaches a maximum when about 2 mg per kg are given, after which the number of waves becomes less. They further observed that the amplitude and frequency of rhythmic contractions were dependent upon the size of the dose administered, and that the frequency was inversely related to the amplitude. Puestow⁸ reported from observations on human patients that morphine stimulated small bowel peristalsis but inhibited or paralyzed the right colon.

From a preliminary study on the motility of the colony of 2 dogs, Templeton and Galapeaux⁹ reported that $\frac{1}{4}$ grain of morphine administered subcutaneously does not materially alter the normal

² Gruber, C. M., Greene, W. W., Drayer, C. S., and Crawford, W. M., *J. Pharm. and Exp. Therap.*, 1930, **38**, 389.

³ Krueger, H., *J. Pharm. and Exp. Therap.*, 1934, **50**, 254.

⁴ Gruber, C. M., and Brundage, J. T., *J. Pharm. and Exp. Therap.*, 1925, **53**, 120.

⁵ Forster, A. C., *Proc. Soc. Exp. Biol. and Med.*, 1938, **38**, 332.

⁶ Gruber, C. M., and Robinson, P. I., *J. Pharm. and Exp. Therap.*, 1929, **37**, 101.

⁷ Krueger, H., Howes, H., and Gay, H., *J. Pharm. and Exp. Therap.*, 1931, **55**, 288.

⁸ Puestow, C. D., *Am. J. Physiol.*, 1938, **123**, 165.

⁹ Templeton, R. D., and Galapeaux, E. A., *Am. J. Physiol.*, 1937, **119**, 414.

activity 24 hours later even after 124 daily injections. They also reported that the immediate effect is an augmentation of activity which lasted for at least 200 minutes. This work has now been extended to include periodic injections of morphine in 2 additional dogs.

The 4 animals used in this study had been under laboratory conditions and used for other colon studies over a period of approximately 2 years. During the training period these animals were required to lie on a cushioned table of the same type and under similar environmental conditions that were to be used in the experimental studies. During this time no efforts were made to prevent ordinary noises and disturbances encountered in the laboratory.

Colon motility was studied by the tandem balloon¹⁰ technic¹¹ previously described. This technic consisted of 2 tandem systems each composed of 3 balloons arranged in a linear order. The balloons which measured 3 cm at the largest diameter and 3 cm in length were spaced 3 cm apart.

The small tubes (3/32 inches in diameter) leading from the balloons were glued together and in the areas where the balloons were tied in place a rubber base was constructed in order to make each balloon an air tight, separate compartment. These tubes leading from the balloons were each connected to water manometers by way of a "T" tube.

For recording motility one set of balloons was inserted by way of the cecostomy into the proximal colon and the second set was inserted by way of the anus into the distal colon. The most proximal balloon was located just distal to the ileocolic sphincter and the most distal balloon just proximal to the internal anal sphincter. The systems were then guyed into place to prevent shifting of the balloons into other segments during the course of an experiment. In order to smooth out the contour of each balloon it was alternately inflated and deflated. Standard inflation was accomplished by drawing 6 cm of water pressure against each balloon. The deflated balloons were clamped out of the circuit and 8 cm of water pressure raised in each manometer. The clamps were then released between the balloons and manometers thus establishing a closed system for recording pressure changes in the balloons.

Certain difficulties are encountered in the study of colon motility which make variations in a planned routine unavoidable. Such factors as trauma from inserting balloons, slight variations in

¹⁰ Templeton, R. D., and Bollens, W. F., *J. Lab. and Clin. Med.*, 1930, **15**, 585.

¹¹ Templeton, R. D., and Lawson, Hampden, *Am. J. Physiol.*, 1930, **96**, 667.

balloon distention, noises, time of feeding, posture of the animal, temperatures of the laboratory, sleep and admonishments make it necessary for the investigator to know the extent to which these experimental variations alter colon motility. After a careful study of experimental variations encountered in the course of an experiment, Templeton and Borkon¹² concluded that the technical variables are of minimal importance when reasonable efforts are made to control the experimental conditions, since more deviation from the usual routine relative to the above factors could be introduced into the procedures without producing a measurable effect.

On the 4 trained animals used 34 control experiments were conducted for the purpose of determining the trend of colon activity to be expected over a 400 minute period. Of the animals used in this study 2 received daily subcutaneous injections of morphine. The other animals were given the same quantity of morphine at weekly intervals. The dosage selected was $\frac{1}{4}$ grain morphine sulphate which had been found in preliminary studies to produce only slight depression on the general condition of the animal. It was observed that usually from 2 to 15 minutes after morphine injections a significant increase in the heart beat and respiration occurred which was of short duration. With this quantity of morphine gastric disturbance seemed to be related to the individual animal. In one of the animals a slight reaction was manifest by slight salivation and a few retching movements. In another animal, vomiting was almost invariable, while in the other 2 these side actions were not apparent.

The usual methods of studying the effects of substances upon the motility of the gastrointestinal tract have been to grossly compare tracings before and after introducing the experimental condition, or to measure the height of manometer excursions and count the number of pressure changes within a given period. In order to obtain a numerical representation of activity which would more adequately express variations from time to time, this method described by Borkon and Templeton¹³ has been followed. A diagrammatic representation of each tracing (Fig. 1) was first transferred to graph paper according to two arbitrary rules. First, the gut was considered active if a contraction or contractions continued for one minute or more. Second, the gut was considered quiet if 2 minutes or more intervened between contractions. By this procedure the active and quiet periods are represented in sharp contrast. The

¹² Templeton, R. D., and Borkon, E. L., *Am. J. Dig. Dis.*, 1939, **5**, 809.

¹³ Borkon, E. L., and Templeton, R. D., *Am. J. Physiol.*, 1937, **118**, 775.

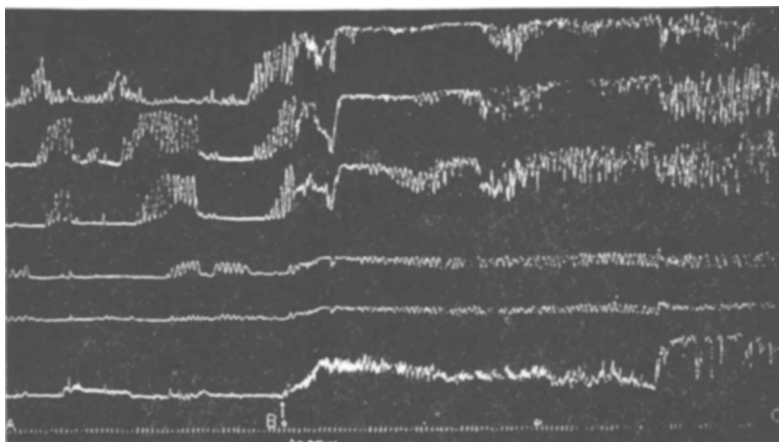


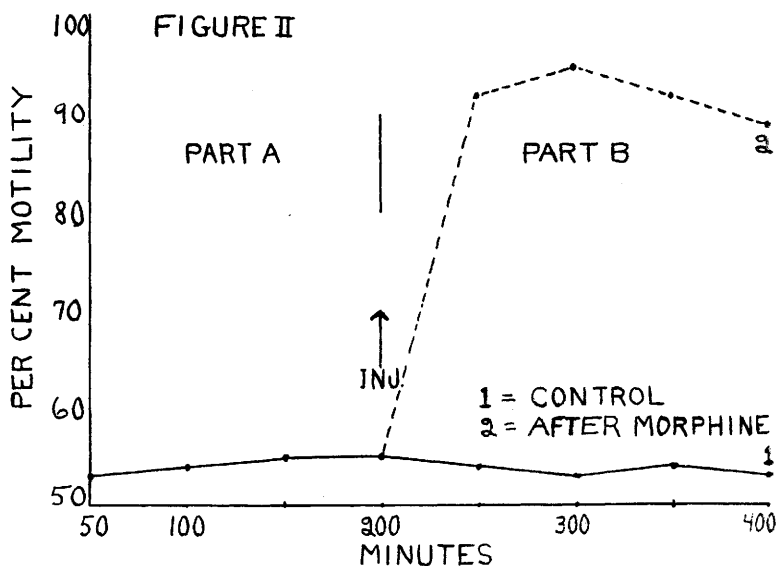
FIG. 1.

A-B—Control Colon Motility.

Arrow—Subcutaneous Injection $\frac{1}{4}$ Grain Morphine.

average quantity of activity per segment of the colon per 50 minute period throughout the course of the experiment was easily obtained from the diagrammatic charts by counting the number of minutes in which all segments were active and dividing the sum by the number of segments recorded. From these data the average per cent of activity per 50 minute period was computed.

In studying the influence of morphine on colon activity two factors must necessarily be considered: (1) the possibility of a cumulative effect which, if influencing colon motility, would be seen in the first 200 minutes of the tracings; and (2) the immediate effect of morphine which would appear in the period immediately following the injection. In considering the first factor the quantity of activity appearing in the colon after a number of daily injections was compared to the quantity of activity observed in the control tracings. The data for this comparison were obtained from the 200 minute control period which preceded morphine injections in the latter part of the study on the 2 animals which received daily injections, and the first 200 minutes of control tracings which preceded the morphine study on the same animals. This comparison revealed (Fig. 2) that the average percentage of activity per 50 minute period in eleven 200 minute tracings taken before the administration of morphine varied between 48 and 57%, while the percentage of activity obtained in 10 tracings after 60 daily injections of morphine and while still receiving daily injections varied between 50 and 60%. This small difference is probably of no significance since



it is well within experimental variation. Another approach to this question would be to compare the influence of prolonged daily injections upon the immediate effect of morphine. From this comparison it was observed that after 60 days of daily injections the average response obtained in 10 experiments was comparable to that which followed the first 10 injections.

From the above data it is apparent that the cumulative effect of morphine within the scope of our experimental time was of dubious importance. Therefore, the second factor, which deals with the immediate effect of morphine must account for the entire physiological disturbance to colon motility following its administration.

Data concerning the immediate effect of morphine on colon activity was obtained from all 4 dogs previously referred to, namely, the 2 animals which received daily injections and the 2 which received weekly injections. Some experiments were obtained on the 2 animals receiving weekly injections in which water was injected subcutaneously instead of morphine. These experiments were considered as controls for the morphine injections and included among the regular control tracings.

A total of 71 experiments were conducted in which the first 200 minutes of each constituted a control period. At the close of this control period $\frac{1}{4}$ grain morphine was injected subcutaneously in 37 experiments while 34 experiments were continued as controls either without injection or with subcutaneous injections of water. In the 200 minute control period the quantity of activity varied from

53 to 57%. In the experimental period the activity in the control experiments varied from 61 to 56%, while the activity of the morphine experiments varied from 89 to 94%. This great increase in activity continuing throughout the 200 minute period which followed morphine injections is characteristic of each experiment.

Summary. 1. The immediate effect of morphine on colon motility resulting from the subcutaneous injection of $\frac{1}{4}$ grain is essentially a marked increase in the tone, with a diminution, frequently a disappearance of quiet periods. 2. Alternating with the periods of high tone is an exaggeration of Type I components of Type II contractions. 3. As far as the colon motility is concerned the dog shows no increased tolerance to $\frac{1}{4}$ grain of morphine given daily. 4. No evidence of a cumulative effect on colon motility was seen to follow daily injections of $\frac{1}{4}$ grain of morphine for a period of 60 days. 5. Twenty hours after subcutaneous injection of $\frac{1}{4}$ grain morphine the colon motility is practically the same as that prior to the injection.

11595

Inhibitory Effect of Quaternary Ammonium Synthetic Detergent on Metabolism of Dental Plaque Material.*

BENJAMIN F. MILLER, JOHN A. MUNTZ AND SIGMUND BRADEL.
(Introduced by G. F. Dick.)

From the Walter G. Zoller Memorial Dental Clinic and the Department of Medicine, University of Chicago.

The carious lesion begins almost invariably on the outer surface of the tooth, *i.e.* under plaque material, and works its way toward the interior. It appears likely that the metabolism of dental plaque material† is intimately associated with the pathogenesis of dental caries. Therefore, it would seem possible to prevent or retard the formation of early lesions if the metabolism of the plaque material could be inhibited completely, or even if it could be reduced to a sub-

* A preliminary report of these experiments was presented before the Subsection on Dentistry of the American Association for the Advancement of Science, Columbus, Ohio, December 30, 1939 (Abstracted in *J. Am. College of Dentists*, 1940, 7, 80).

† "Plaque material" is the thin film, composed of bacteria embedded in organic substance, which remains on the surface of the teeth after swabbing with cotton and washing with a stream of water.