SECTIONS

CAFFEINE EFFECTS UPON THE ACTIVITY OF THE LONGITUDINAL MUSCLES OF THE SMALL INTESTINE.[1]

BY RALPH H. CHENEY.[2]

An extensive literature has dealt with the effect of various substances upon the spontaneous activity and upon the normal physiological state of the small intestine. Prior to 1916, many investigators aided in the development of methods and reported generalities which made possible the more detailed studies with reference to specific effects upon the several levels of the gut and upon the longitudinal and circular musculature separately. A series of illuminating studies which have significance to the present study, began about 1916 by Salant and Mitchell ('16) on the heavy metals, Salant and Schwartze ('17) on sodium citrate, Taylor and Alvarez ('17) on temperature effects, Alvarez ('18a) on differences in the behavior of different levels of the intestine, Alvarez (18b) on the effects of drug action upon intestinal rhythmicity and Kruse ('19-'20) on the action of bromide.

Since 1920, the effects of a greater variety of substances upon the intestine and upon smooth muscle generally have been reported. Müller ('21) published a series of photomicrograms to illustrate the nerves of the intestinal wall. Frédericq and Mélon ('23) reported the caffeine-adrenalin antagonism with reference to intestinal motility. The isolated duodenal segments of the rabbit were used as the experimental material. King and Arnold ('22) discussed the activities of the intestinal mucosal motor mechanism. They concluded that the intestinal mucosa stimulation was a local reaction and myogenetic in origin. The rôle of a change in p_H in the regulation and control of the motor activities of the small intestine was emphasized by Hammett ('22). Evans and Underhill ('23) also dealt with p_H effects on the tonus and contractions of smooth muscle. Gross and Clark ('23) reported the influence of the oxygen supply on the response of the isolated intestine to drugs. The work of Henderson ('23) on atropin effects, Roth ('23) on barium chloride action, Crane and Henderson ('24) on the sensitivity to internal pressure, the extensive study by La Barre ('24) on opium alkaloids, by Tiegs ('24, '25) on the nerve net and its relation to the automatic rhythmic movements of plain muscle in the frog's stomach, by Burnett ('25) on variations in the intestinal rate, and the reports by Rademaekers and Sollmann ('24) added considerable specific data to the general problem of the pharmacology of the intestine.

Between 1925 and 1930, informative contributions were made by D'Haenens ('25) on eserine and atropin, by Alvarez ('25) on the slow tonus rhythm in the bowel, by De Boer, Dreyer and Clark ('25) on the several constituents of the body

[1] From the laboratories of the Brooklyn College of Pharmacy, L. I. University, Brooklyn, New York, and the Marine Biological Laboratory, Woods Hole, Mass.

[2] Professor of Biology, Long Island University.

fluids which act as plain muscle stimulants, by Gruber ('26) reporting that narcotics cause a loss of tonus of excised strips of plain muscle, by Polansky ('27) on yeast extract effects, by Sollmann ('27) on the effect of mechanical and physical conditions upon the response of the rabbit's ileum, by whitehead ('29) on the responses of the excised rabbit intestine to alterations of electrolytic concentrations, by von Oettingen ('29) on the simultaneous cinematography of intestinal movements and tracings, by Frédericq ('30) on chronaxie, and by Waucomont ('30) in an extensive article on the general pharmacology of the intestine of the rabbit and dog.

Since 1930, many articles have dealt with the pharmacology and physiology of smooth muscle and of the intestine in particular. Papers of special importance during this period with reference to the current report have been published by Komant ('32) dealing with the stimulating action of caffeine, theobromine and theophylline, by Salant and Parkins ('32) on ergotamine and ion influences, by Rabbeno and Cisbani ('32) on the digestive tube pharmacology in the frog, by Epstein ('33) on the response of the alimentary tract to autonomic drugs, by Hockett, Newman and Thienes ('33) on the reciprocal activity of the muscular coats of the guinea pig, by Hoyt, Patek and Thienes ('34) with the beginning of a series of articles on smooth muscle action, and by Emerson ('36) on the biochemical effect of ether on the gut. In 1937, a number of valuable contributions included a paper by Van Liere and Emerson ('37) on the absorption of digitalis from the small intestine during anoxemia, and one by Reynolds ('37) on smooth muscle action in a study of the control of uterine contractility. A preliminary statement was made by Cheney ('37) of my present studies of the caffeine effects upon the myenteric activity in the rabbit.

Donatelli ('38) discussed a new cannula for smooth-muscled tubular organs and described a system for recording the activity of the circular and longitudinal muscles simultaneously with relative ease. Several papers on smooth muscle have been published by Singh ('38) studying the properties of tonic contraction in smooth muscle, by Fischer ('38) on invertebrate smooth muscle birefringence, by Farmer ('38) on the inhibitory action of narcotics on the histamine contraction of the plain musculature of the guinea pig, by McLachlin ('38) on the action of ergometrine on the isolated human uterus, by Lazarus ('38) on the action of urea upon the small intestine of the rabbit, and a particularly significant paper by Beard and Pizzolato ('38) involving the effect of caffeine upon the creatine-creatinine metabolism which is of interest to the explanation of muscle physiology and pharmacology generally. An article by Franklin and Maher-Loughnan ('38) on the circular musculature of the small intestine of the cat throws some light upon the behavior upon the longitudinal muscles. Eichler's ('38) recent volume, "Kaffee und Koffein" primarily reviews the literature from 1920 to 1938 and includes brief data and references to the effects upon the intestine.

With a few exceptions such as the report by Plant and Reynolds ('22) who noted the improvement of peristaltic movements with caffeine, and the more recent paper by Komant in 1932, recent researches have not dealt specifically and in detail with the influence of caffeine upon myenteric activity. The current paper gives evidence of the effect of the purine complex, caffeine, following its absorption through the mucosa, upon the intrinsic muscular motility of the isolated segments

of the small intestine of the rabbit. Individual and comparative sensitivities of three regions of the gut are discussed with reference to the response of their longitudinal musculature during and after caffeine perfusion. The phenomena of rhythmicity, rate, tonus and amplitude are shown for each region studied by means of kymographic records.

GENERAL METHOD.

Animals were sacrified by a blow on the occiput in order to avoid any anesthetic effect. Only actively rhythmic segments were employed because it has been pointed out by Hooker ('12) that rhythmic and arrhythmic segments respond differently to the *same* stimulus. In addition, specifically comparable regions were used: namely, the proximal descending duodenum, the mid jejunum and the proximal ileum. This precaution was necessary in accordance with the study by Magee and Southgate ('28) on salt effects and their demonstration of the fact that considerable difference exists—the degree of sensitivity of the several levels of the gut to the same chemical substance.

A study of various recording methods was made as given by Abderhalden ('29) and especially of the methods employed by Trendelenburg ('13,' 17), by Plant and Reynolds ('22), by Sollmann and Rademaekers ('26), by Salant and Brodman ('29) and by Bernheim ('33). A modification of the Trendelenburg apparatus was chosen for recording the longitudinal contractions on the basis of the required accuracy within the limits of the preparation used, practicability, definiteness and reproducibility of experimental results. It was essentially the modification employed by Polansky ('27) but arranged for the recording of the longitudinal musculature only.

The common rabbit (Lepus) was used. Maintenance of uniform conditions for the perfusion of caffeine through the lumen of the isolated segment was attained with regard to the preparation of the nutrient medium, the experimental medium, pressure, temperature, oxygenation, time intervals, p_H and recording mechanics. These controls of the apparatus and the procedures exercised in the preparation of the experimental material were in accordance with the requirements indicated by the investigations referred to in the literature cited previously.

EXPERIMENTAL PROCEDURE.

1. Non-excited animal sacrificed by a blow on the occiput. (The animal had not been fed for 24 hours but fed a few minutes prior to death.) Desanguinated immediately *via* carotid artery and jugular veins.

2. Following a long anterior-posterior incision along the mid-ventral line, the donor's viscera was exposed and an actively rhythmic segment 6 to 7 cm. long was removed with precision from the desired area. When attached to the apparatus, an actively rhythmic length of 4 cm. was employed uniformly.

3. Segments were handled with precautions not to cause mechanical pinching or other stimulation. Placed in a paraffined petri dish flooded with mammalian Tyrode's solution at 38° C. and buffered to p_H 7.55, the segment was pressed gently from the proximal (or oral) end to the distal (or cæcal) termination to remove any contents of the lumen. Then a pipette caused the warm Tyrode to gently flood the lumen in the same direction thereby washing thoroughly and preventing auto-intoxication.

4. Attachment to perfusion apparatus by flared glass cannulas so that the perfusion would flow in the same (its normal) direction.

5. Adjustment of mechanical, electrical and thermal units for uniform experimental conditions regarding the factors mentioned. The excised segment was allowed to contract rhythmically under approximately natural conditions in a warm bath of oxygenated Tyrode's solution.

6. Recording of longitudinal contraction by means of a bees-waxed, silk thread from the preparation to the writing lever was allowed to proceed until normal behavior was observed in all details.

7. Changes in perfusion fluids could be accomplished at any moment by means of a two-way stop-cock.

DISCUSSION.

Direct excitation of all intestinal smooth muscle by nerves is improbable because there are more muscle cells than there are nerve fibers. The intestine, however, possesses abundant nerve plexuses within its walls. The subserous, myenteric plexus of Auerbach with its network of fibers and cells between the longitudinal and circular muscles and the submucosal plexus of Meissner are well known. Moreover, the ganglion cells of Auerbach's plexus serve as the ganglionic cells for vagus connections and possibly for the sympathetic nervous system. Undoubtedly, the extrinsic plexis is involved normally in the stimulation and control of the intestinal motility and functions as an additional safety factor as suggested by Thomas and Kuntz ('26) and by Henderson ('28). The extrinsic nerve supply, however, can be eliminated and intestinal motility will persist. Alvarez and Mahoney ('22) and Gasser ('26) have shown that smooth muscle even when it is devoid of *all* nervous elements maintains a spontaneous rhythm and tonus.

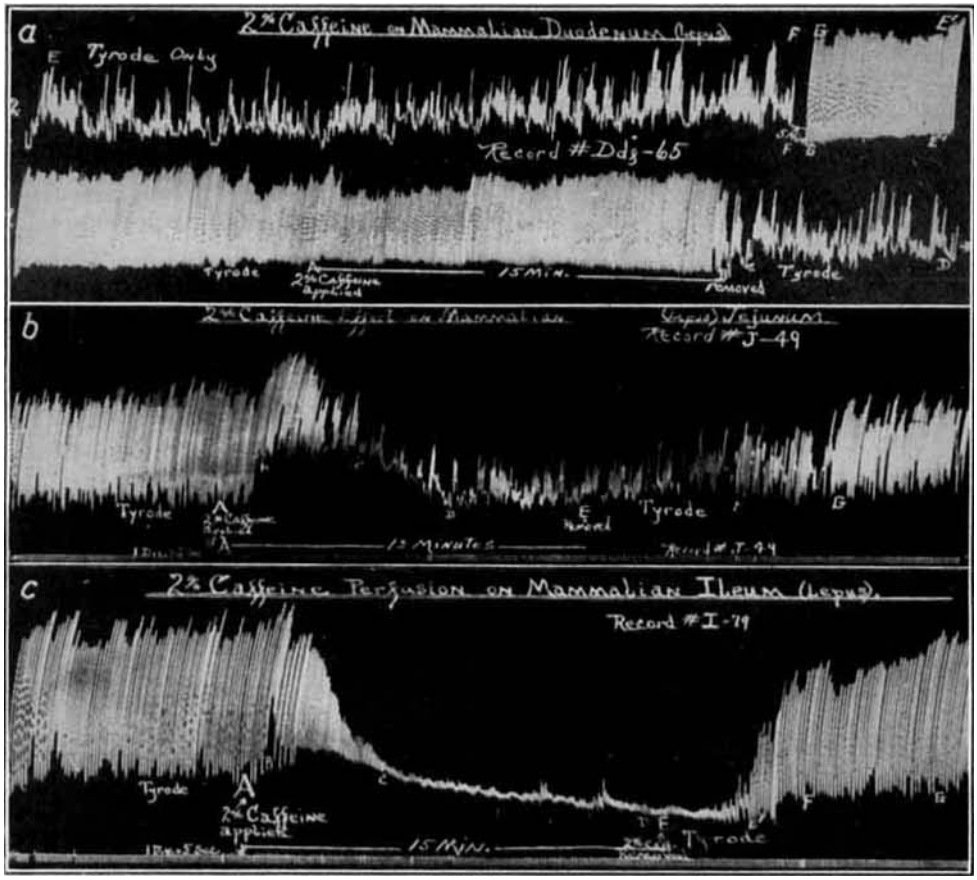

Fig. 1.—Effect of Caffeine (2%) upon the Intrinsic Myogenetic Responses of the Longitudinal Musculature of the Rabbit Intestine. (*a*) Duodenum Record No. Ddf–65. (*b*) Jejunum Record No. J–49. (*c*) Ileum Record No. I–79.

Moreover, Swirski ('02) demonstrated that the excitation of the intestinal motility depends upon fiber to fiber excitation by mechanical distension and upon the *nature* of the lumen contents. It is known that smooth muscle is more susceptible to *chemical* excitation than is skeletal muscle. In view of these facts, my procedure here permits the observation and comparison of the effects of caffeine in different concentrations upon the longitudinal musculature of similar segments. The

perfusion solutions used were as follows: 2%, 1%, 0.5%, 0.1%, 0.05% pure caffeine, alkaloid, U. S. P. Powder (Merck).

As pointed out by Verzár and McDougall ('36) in their monograph, the purines are absorbed normally by the blood vessels as they are not present in the lymph. Obviously, it is apparent that, with the elimination of the circulatory distribution of the caffeine and with the decentralization of nervous control in the preparation which I employed, the contact between the longitudinal musculature and the caffeine was possible only by absorption through the mucosa and subsequent diffusive distribution. It should be noted also that Šiaulis and Sollmann ('26, '27) concluded that the longitudinal and circular muscle layers contract independently; and that, although the contractile force of one muscle layer may stimulate the other to contract, there is no absolutely dependent correlation between the two sets of muscles. Therefore, it is possible to record the action of either set separately with the apparatus and preparation employed under the conditions of the experiments which I am reporting here. It should be appreciated, however, that the observations derived from the excised segment do not preclude the possibility that some neuro-muscular coördination may exist in the intact animal.

The preparation utilized in this study has certain definite limitations with regard to the transfer of the results "in toto" to the intact intestine. It has also the desirable elimination of various complicating factors regarding the observation of direct caffeine effects. It furnishes a favorable intestinal muscle-preparation for the study of modifications in the muscular activity due to the variation of a single chemical complex—in this case, caffeine—in the perfusing fluid. The alterations in the normal behavior of such a segment are a convenient measure of the direct myogenetic effects in response to a given substance.

For the sake of brevity and because of the fact that only the concentrated solutions of caffeine are consistently effective, only the 2% caffeine effects are presented by their kymographic records on each of the three levels of the small intestine. (See Fig. 1.) The responses of comparable segments to the perfusion by other percentages of caffeine are condensed in Table I. The data derived from the *individual* effects of five different percentages of caffeine upon the *same* intestinal area, gives the basis for a comparison of the sensitivities between the *several* areas which were subjected to the same series of caffeine perfusions.

TABLE I.—COMPARATIVE SENSITIVITY OF INTESTINAL AREAS TO CAFFEINE.

Comparative Sensitivity (all factors considered).

Key: 1. First effective; most effective; first recovery.
2. Next in order.
3. Least or last in order.

% Caffeine in Perfusion Solution.	Intestinal Segment.	Order of First Effect.	Degree of Effect.	Order of Recovery.	Final Recovery Complete or Incomplete.
2%	Duodenum	3	3	3	Complete
	Jejunum	2	2	2	Complete
	Ileum	1	1	1	Complete
1%	Duodenum	3	3	1	Complete
	Jejunum	2	2	2	Complete
	Ileum	1	1	3	Complete
0.5%	Duodenum	1	1	2	Complete
	Jejunum	3	2	3	Complete
	Ileum	2	3	1	Complete
0.1%	Duodenum	No effect	...	...	...
	Jejunum	Effective	Slight	Rapid	Complete
	Ileum	No effect	...	...	...
0.05%	Duodenum	No effect	...	...	...
	Jejunum	No effect	...	...	...
	Ileum	No effect	...	...	...

An examination of Fig. 1 reveals the actual variations in the activity of the longitudinal musculature of the rabbit which were produced by perfusing the duodenal, jejunal and ileal segments with 2% caffeine-in-Tyrode solutions.

Record No. Ddf-65 demonstrates the effect upon the duodenum. Normal behavior is recorded from the left end of the lower line up to point "A" when the caffeine perfusion began and was continued for a fifteen minute period. A very slight tonus improvement may be noted which is accompanied by an amplitude decrease. Both effects were corrected at somewhat less than the half-way period of the perfusion. With the removal of the caffeine and the substitution of the normal nutrient Tyrode solution at "B," a delayed caffeine effect began to develop, an improved tonus and reduced amplitude effect rapidly becoming drastic between "B" and "C," persisting through the time interval from "B" to "F" inclusive. Full recovery occurred during the five minute interval from "F" to "G." The recovery occurs more abruptly than the original variations appear in the normal.

Record No. J-49 shows the effect upon the jejunum. With the caffeine applied at "A," an effective variation occurs more promptly than in the duodenum. Moreover, the tonus increase and amplitude decrease do not occur simultaneously. At "B" a drastic tonus improvement occurs suddenly but the amplitude decrease does not appear until the mid-way time interval between "B" and "C." With the development of the drastic amplitude reduction at "C," the tonus level falls rapidly to approximately the normal level and is maintained during the remainder of the perfusion period whereas the amplitude depression persists to point "G" when approximately full recovery occurs. The caffeine effect develops more rapidly in the jejunum than in the duodenum and the recovery time is much less in the jejunum.

Record No. I-79 presents the effect upon the ileum. Following the application of caffeine at "A," an improved tonus and a decreased amplitude develop rapidly in approximately the same time interval as in the jejunum. The tonus improvement is proportionately less than in the jejunum and the amplitude decrease is proportionately more than in the jejunum. With the cessation of the caffeine perfusion and the return of the normal nutrient Tyrode at "E," the drastic variation in the normal behavior persists to "É," when a rapid recovery begins which becomes full recovery between "F" and "G." This complete recovery is appreciably more rapid in the ileum than in the jejunum and much more rapid than in the duodenum.

CONCLUSIONS.

1. The three regions of the mammalian small intestine possess individual and different sensitivities with respect to their intrinsic motility in response to the caffeine stimulation of the longitudinal muscles.

2. Since complete recovery occurs, even after perfusion with 2% caffeine solutions (2.2% would be saturation), in each of the three primary levels of the gut and since the effect of lower percentages is variable, no part of the small intestine can be described as highly sensitive to the action of caffeine.

3. From a study of the kymographic records which were obtained from 150 experiments,[1] it is evident that the degree of tonicity and the amplitude of contraction were affected by caffeine to a greater extent than is indicated by any variation in the rhythmicity or rate, which was negligible. The tendency in all three segments is to improve the tonus and decrease the amplitude temporarily of the longitudinal musculature in each case. It is of interest that caffeine affects the tonicity in view of the fact that the exhibition of tonus when separated from the central nervous system is one of the chief behavioristic differences between smooth and striated muscle. Caffeine affects the smooth muscle of the intestine directly as it is known to do in both striated and cardiac muscle.

4. In accordance with the general observations of Alvarez and Mahoney ('22) that the gastro-intestinal tract shows decreasing gradients from the oral to the anal (cæcal) termination with reference to rhythmicity, frequency of contractions

[1] I take this opportunity to thank my former research assistant, Mr. Isador Shaw, for his careful manipulation of the apparatus and of the preparations throughout these investigations.

and the metabolic rate, it might be presumed that the caffeine effects upon these factors would follow a similar sequence. Such a correlation does not exist. There is no absolute gradient for the time or degree of caffeine effects or for the rate of recovery in the longitudinal musculature of the small intestine. The separate intestinal areas, however, demonstrate a distinct difference in the degree of their sensitivity to a given concentration of caffeine.

5. It is suggestive that the combined effects of caffeine upon the myogenic activity of the longitudinal musculature of the intestine are such that the absorption of caffeine from the lumen may improve the physical factors of pressure and movement. Thereby, the process of the absorption of nutrients from the lumen would be facilitated.

LITERATURE CITED IN CHRONOLOGICAL ORDER.

(1) Swirski, *Naunyn-Schmiedebergs Arch. f. exper. Path. u. Pharmakol.*, 48, 282 (1902).
(2) Hooker, *Am. J. Physiol.*, 31, 47 (1912).
(3) Trendelenburg, *Ztschr. f. Biol.*, 61, 67 (1913).
(4) Salant and Mitchell, *Am. J. Physiol.*, 39, 355 (1916).
(5) Salant and Schwartze, *J. Pharmacol. and Exp. Therap.*, 9, 497 (1917).
(6) Taylor and Alvarez, *Am. J. Physiol.*, 44, 344 (1917).
(7) Trendelenburg, *Naunyn-Schmiedebergs Arch. f. exper. Path. u. Pharmakol.*, 81, 55 (1917).
(8) Alvarez, *Am. J. Physiol.*, 45, 342 (1918*a*).
(9) Alvarez, *Ibid.*, 46, 554 (1918*b*).
(10) Kruse, *J. Pharmacol. and Exp. Therap.*, 14, 149 (1919–1920).
(11) Müller, *Upsala Läkarenf. Forh.*, 26, 1 (1921).
(12) Plant and Reynolds, *Proc. J. Pharmacol. and Exper. Therap.*, 19, 256 (1922).
(13) Alvarez and Mahoney, *Am. J. Physiol.*, 59, 421 (1922).
(14) Frédericq and Mélon, *Compt. rend. Soc. de biol.*, 87, 92 (1922).
(15) King and Arnold, *Am. J. Physiol.* 59, 97 (1922).
(16) Hammett, *Ibid.*, 60, 52 (1922).
(17) Evans and Underhill, *J. Physiol.*, 58, 1 (1923).
(18) Gross and Clark, *Ibid.*, 57, 457 (1923).
(19) Henderson, *Arch. de internat. Pharmacodyn. et de Thérapie*, 27, 205 (1923).
(20) Roth, *Ibid.*, 27, 333 (1923).
(21) Crane and Henderson, *Am. J. Physiol.*, 70, 22 (1924).
(22) La Barre, *Arch. de internat. Pharmacodyn. et de Thérapie*, 29, 179 (1924).
(22a) Rademaekers and Sollmann, *Ibid.*, 29, 481 (1924).
(23) Tiegs, *Australian J. Exper. Biol. and M. Sc.*, 1, 131 (1924).
(24) Tiegs, *Ibid.*, 2, 157 (1925).
(25) Burnett, *J. A. M. A.*, 85, 1777 (1925).
(26) D'Haenens, *Ibid.*, 30, 77 (1925).
(27) Alvarez, *Am. J. Physiol.*, 74 ,181 (1925).
(28) De Boer, Dreyer and Clark, *Arch. de internat. Pharmacodyn. et de Thérapie*, 30, 141 (1925).
(29) Abderhalden, *Handb. biol. Arbeitsmeth., Abt. V, Teil 5A, Heft* 5, 843 (1929).
(30) Sollmann and Rademaekers, *Arch. de internat. Pharmacodyn. et de Thérapie*, 31, 39 (1926).
(31) Thomas and Kuntz, *Am. J. Physiol.*, 76, 606 (1926).
(32) Gasser, *J. Pharmacol. and Exper. Therap.*, 27, 395 (1926).
(33) Šiaulis and Sollmann, *Arch. de internat. Pharmacodyn. et de Thérapie*, 32, 340 (1926).
(34) Gruber, *J. Pharmacol. and Exper. Therap.*, 30, 149 (1926).
(35) Šiaulis and Sollmann, *Am. J. Physiol.*, 81, 579 (1927).
(36) Sollmann, *Ibid.*, 81, 579 (1927).
(37) Polansky, *Ibid.*, 83, 488 (1927–1928).

(38) Henderson, *Am. J. Physiol.*, 86, 82 (1928).
(39) Magee and Southgate, *J. Physiol.*, 65, Proc. VII (1928).
(40) Whitehead, *Am. J. Physiol.*, 89, 253 (1929).
(41) von Oettingen, *Ibid.*, 90, 464 (1929).
(42) Salant and Brodman, *J. Pharmacol. and Exper. Therap.*, 37, 55 (1929).
(43) Frédericq, *Arch. de internat. Pharmacodyn. et de Thérapie*, 38, 438 (1930).
(44) Waucomont, *Ibid.*, 36, 285 (1930).
(45) Komant, *Naunyn-Schmiedeberg's Arch. f. exper. Path. u. Pharmakol.*, 163, 635 (1932).
(46) Salant and Parkins, *J. Pharmacol. and Exper. Therap.*, 45, 315 (1932).
(47) Rabbeno and Cisbani, *Arch. de internat. Pharmacodyn. et de Thérapie*, 43, 268 (1932).
(48) Epstein, *Ibid.*, 45, 251 (1933).
(49) Bernheim, *Am. J. Physiol.*, 104, 433 (1933).
(50) Hockett, *Newman and Thienes, Arch. de Pharmacodyn. et de Thérapie*, 46, 363 (1933).
(51) Hoyt, Patek and Thienes, *Ibid.*, 47, 228 (1934).
(52) Verzár and McDougall, "Absorption from the Intestine," Longman's, Green and Co., London (1936).
(53) Emerson, *Proc. Soc. Exper. Biol. and Med.*, 35, 376 (1936).
(54) Van Liere and Emerson, *Arch. de internat. Pharmacodyn. et de Thérapie*, 57, 45 (1937).
(55) Reynolds, *Physiol. Rev.*, 17, 304 (1937).
(56) Cheney, *Proc. Soc. Exper. Biol. and Med.*, 37, 572 (1937).
(57) Donatelli, *Arch. de internat. Pharmacodyn. et de Thérapie*, 58, 27 (1938).
(58) Singh, *J. Physiol.*, 94, 1, 322 (1938).
(59) Fischer, *J. Cellular and Comp. Physiol.*, 12, 85 (1938).
(60) Farmer, *Proc. Soc. Exper. Biol. and Med.*, 39, 204 (1938).
(61) McLachlin, *J. Pharmacol. and Exper. Therap.*, 64, 243 (1938).
(62) Lazarus, *J. Physiol.*, 93, Proc. 32-P (1938).
(63) Beard and Pizzolato, *J. Pharmacol. and Exper. Therap.*, 63, 306 (1938).
(64) Franklin and Maher-Loughnan, *J. Physiol.*, 94, 426 (1938).
(65) Eichler, Kaffee und Koffein, *Verlag von J. Springer*, Berlin, 58, 91 (1938).

A STUDY OF THE STABILITY OF ALKALOIDAL POISONS IN THE PRESENCE OF PRESERVATIVES.*

CHARLES O. WILSON[1] AND L. W. RISING.[2]

The stability of alkaloids under various conditions has been the subject of many investigations. Among the more important of these are the very few studies undertaken in the interest of forensic medicine. These deal primarily with the fate of alkaloids when in contact with dead tissue, either preserved with one of several common preserving materials or allowed to decompose. The conditions of contact between the alkaloid and contaminating substance were generally controlled to simulate as nearly as possible one or more actual toxicological situations. One of the earliest investigations of this type carried out was by Tidy (1) who studied the durability of morphine sulfate when exposed to the processes of tissue decomposition within the human body. Little significant work on the stability of alkaloids under circumstances involving legal toxicological investigation has been done since. The recent studeis of Rising and Lynn (2, 3, 4, 5), while dealing in part with alkaloids, were principally on poisons of non-alkaloidal nature.

---

* Presented before the Scientific Section, A. PH. A., Minneapolis meeting, 1938.

[1] Assistant Professor of Pharmaceutical Chemistry, George Washington University, School of Pharmacy, Washington, D. C.

[2] Professor of Pharmacy, University of Washington, Seattle, Wash.