EVALUATION OF ORAL DILUTION AS
A FIRST AID MEASURE IN POISONING

by

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ABSTRACT

Dilution with large volumes of water is a widely recommended first aid measure for the treatment of poisoning from ingested chemical agents. In view of the lack of experimental work to support its clinical application and in view of possible adverse effects that may attend its use, further investigation was undertaken to determine the influence of oral dilution on blood levels of pentobarbital sodium, quinine hydrochloride, and aspirin. The results indicate that oral dilution with large volumes of water increases the rate and degree of gastrointestinal absorption of pentobarbital and quinine, although it has no significant effect on the absorption of aspirin. In view of the possibility of enhanced gastrointestinal absorption of certain chemicals caused by oral dilution, it is suggested that this procedure not be employed as a first aid treatment for ingested systemic poisons.

I. INTRODUCTION

Each year an estimated one-half to one million people accidentally ingest medicines and household products (Verhulst, Crotty and Maisel 1966). Only a portion of these cases are ever reported to the National Clearinghouse for Poison Control Centers. An analysis shows medication is the causative agent in one-half of these cases (Verhulst et al 1966). Children under five years of age are involved in 50% of all cases (Jacobziner 1962), and, in fact, for the years 1961-62, the incidence was 86% (National Clearinghouse for Poison Control Centers Bulletin 1963).

In the seven years since 1958, a total of 10,440 cases have been reported to the Arizona Poisoning Control Information Center. In contrast to the national averages, medications are the causative agent in 64% of the total cases. Indeed, in 1965, 72.3% of the 1791 cases of poisoning involved medicines. Considering the age of the individual, 65.7% are composed of children under five (Arizona Poisoning Control Information Center, unpublished data) which is above the national average.

Since ingestion of noxious materials can result in toxic effects on the body, a first aid treatment has been sought to prevent the absorption of the substance from the gastrointestinal tract. Dilution with large volumes of water or other fluids is widely recommended as a first aid measure for the treatment of poisoning from ingested chemical agents (American Red Cross 1957, Dreisbach 1963, Flint 1964).

This procedure is based on the belief that dilution will slow absorption of a chemical from the gastrointestinal tract by increasing the amount of fluid that must be absorbed for a given amount of poison (Dreisbach 1963). However, no experimental evidence has been presented to support this view. Indeed, a study by Ferguson (1962) showed that oral median lethal doses (LD50s) of a number of drugs in rats vary inversely with the volume of water in which a drug is administered. In contrast to the above view, the observations of Ferguson would seem to imply that dilution of an ingested chemical may enhance rather than retard its absorption from the gastrointestinal tract.

In view of the lack of experimental work to justify the use of oral dilution in poisoning and the possible adverse effects that may attend its use, further investigation of this recommended procedure seems warranted. The present investigation was designed to determine the influence of oral dilution on blood levels of certain chemical agents, since the blood concentration of a chemical compound is related to its rate of absorption from the gastrointestinal tract. Pentobarbital sodium, quinine hydrochloride, and aspirin were selected as representative chemical compounds for this project. Pentobarbital is absorbed from the stomach (Schanker et al 1958, Schanker 1962) and small intestine (Schanker et al 1958, Schanker 1962, Wilson 1962, Schanker 1963). Quinine is predominantly absorbed from the small intestine (Hillman and Harpur 1961, Brodie 1964, Rollo 1965). Aspirin is considered to be readily absorbed from both stomach and small intestine (Schanker 1962, Levy 1963, Martin 1964). The results obtained constitute the basis of this thesis.

II. EVALUATION OF ORAL DILUTION WITH WATER ON THE ABSORPTION OF PENTOBARBITAL, QUININE AND ASPIRIN

A. Pentobarbital

Introduction:

The barbiturates are the causative agent in 9.7% of the total cases of poisonings in Arizona since 1958 (Arizona Poisoning Control Information Center, unpublished data). Nationwide, they are responsible for half of all accidental deaths from drugs (Cann, Neyman and Verhulst 1958).

Pentobarbital sodium is a short-acting barbiturate very commonly prescribed by physicians. When given orally, it is absorbed from the stomach (Schanker et al 1958, Schanker 1962, Maynert 1965) and intestine (Schanker et al 1958, Schanker 1962, Wilson 1962, Schanker 1963, Maynert 1965). In humans, blood concentrations of 1.0 to 2.5 mg. per 100 ml. will produce coma while death results from levels of 1.5 to 7.5 mg. per 100 ml. (Thienes 1964). The symptoms of acute poisoning from a barbiturate include sleepiness, mental confusion, coma, and respiratory depression (Cumming 1961, Dreisbach 1963, Price and Dripps 1965, Maynert 1965). One can observe most of these same symptoms in rats and they are consistent with the blood pentobarbital concentrations.

Experimental:

Female Sprague-Dawley rats, weighing 200 to 275 grams, were fasted for 24 hours and divided into test and control groups of five to eight animals. The animals were allowed free access to water except

the last hour prior to testing. Pentobarbital sodium, 25 mg./Kg., calculated as the base, was given by oral intubation in a volume of 2 ml./Kg.: one minute later, the control animals were administered a small volume of water (1 ml./Kg.) by gavage, and the test animals were administered a large volume of water (20 ml./Kg.). At 10, 20, 40, 80, 160, and 320 minutes following drug treatment, the animals were anesthetized with ether and blood samples were collected from the abdominal aorta for analysis by the method of Goldbaum (1948) as modified in this laboratory (Picchioni et al 1966) and described in Appendix A.

Results:

The results of the pentobarbital study are given in Table 1 and Figure 1. Ten minutes after the administration of pentobarbital, the blood concentration of the drug in test animals was 33% higher than in control animals, but the difference is not statistically significant ($p > 0.05$). At the 20- and 40-minute time periods, the pentobarbital levels were 90 and 78% greater than those of the corresponding control animals, respectively. These elevated blood levels of pentobarbital are significantly higher than the control levels ($p < 0.01$). By the 80-, 160-, and 320-minute time periods, the blood pentobarbital levels of the test animals were similar to those of the corresponding test animals ($p > 0.05$).

Discussion:

Oral dilution with water is presumed to delay the absorption of noxious substances from the gastrointestinal tract (American Red Cross 1957, Dreisbach 1963). However, the results of the pentobarbital

Table 1. The effect of oral dilution on blood pentobarbital concentrations

Time after drug administration (minutes)	Control Animals (mg./100 ml.)	Test Animals (mg./100 ml.)
10	1.2 (0.98-1.5)	1.7 (1.4-1.9)
20	1.0 (0.8 -1.3)	1.9 (1.7-2.2)
40	1.8 (1.5-1.97)	3.2 (2.0-3.4)
80	1.7 (1.5-1.9)	1.6 (1.4-1.8)
160	1.3 (1.1-1.5)	1.5 (1.3-1.7)
320	0.8 (0.7-1.0)	0.9 (0.7-1.0)

Figure 1. The effect of oral dilution on blood pentobarbital concentration. Bracketed lines represent 95% confidence limits.

study indicate that oral dilution with large volumes of water increases the rate and degree of gastrointestinal absorption of pentobarbital.

Several factors can influence the absorption of pentobarbital. Since barbiturates are absorbed from the intestine (Schanker et al 1958, Schanker 1962, Wilson 1962, Schanker 1963, Maynert 1965) as well as from the stomach (Schanker et al 1958, Schanker 1962, Maynert 1965), by nonionized diffusion (Schanker 1963, Brodie 1964), gastric emptying time probably has only a slight effect on the absorption of pentobarbital. Hence, the important effect of the large volume of water administered to the test rats very likely consists of an increase in the surface area for absorption in the stomach and intestine. It is interesting to note that consistent with their blood pentobarbital levels, the test animals were considerably more ataxic than the corresponding control animals during the 10-, 20-, and 40-minute test periods.

The large volume of water administered to the test animals results in rapid and more complete absorption, while the small volume of water administered to the control animals allows the rate of absorption to be slower. This would account for the almost identical blood levels in the control animals at both the 40- and 80-minute time intervals, while the test animals showed a considerable decline in blood concentration between the 40- and 80-minute intervals.

Consequently, in the case of an overdosage of pentobarbital, a large volume of water enhances absorption of the drug and thereby intensifies the toxic effects.

II B. QUININE

Introduction:

Quinine hydrochloride, an alkaloid, is not absorbed from the stomach (Schanker 1962, Brodie 1964) following oral administration but is readily absorbed from the small intestine (Hillman et al 1961, Brodie 1964, Rollo 1965) and reaches maximum blood levels in one to three hours (Rollo 1965). The symptoms resulting from acute poisoning include hypotension, vomiting, cardiac irregularities, blurring of vision and tinnitus (Dreisbach 1963, Becker 1963, Rollo 1965). None of these symptoms can be observed in rats but plasma quinine concentrations can be easily determined.

Experimental:

Female Sprague-Dawley rats, weighing 185 to 195 grams, were fasted for 24 hours and divided into control and test groups of five to nine animals. The animals were allowed free access to water except during the last hour prior to testing. Quinine hydrochloride, 100 mg./Kg., calculated as the base, was given by oral intubation in a volume of 2 ml./Kg.; one minute later the control animals were administered a small volume of water (1 ml./Kg.) by gavage and the test animals were administered a large volume of water (20 ml./Kg.). At 15, 60, and 120 minutes after drug treatment, a control group and a test group of animals were anesthetized with ether and blood samples were collected from the abdominal aorta for analysis of plasma quinine concentrations by the

fluorometric procedure of Brodie and Udenfriend (1943) and described in Appendix B.

Results:

The results of the quinine study are presented in Table 2 and Figure 2. At the 15-, 60-, and 120-minute time periods the plasma quinine levels in the test animals were 138, 72, and 62.5% higher than those of the corresponding control animals, respectively. These values are statistically significant ($p < 0.05$).

Discussion:

Oral dilution with water is presumed to delay absorption of noxious substances from the gastrointestinal tract (American Red Cross 1957, Dreisbach 1963). However, the results of the quinine study indicate that oral dilution with a large volume of water increases the rate and degree of gastrointestinal absorption of quinine.

Quinine is poorly absorbed from the stomach (Schanker 1962, Brodie 1964) but is readily absorbed from the small intestine (Hillman et al 1961, Brodie 1964, Rollo 1965). Hence, hastening the transfer of the drug into the intestine by oral dilution would tend to allow intestinal absorption to start earlier in the test animals than in the control animals. However, the main contribution of oral dilution to the higher plasma quinine levels in the test animals is probably due to an increase in the surface area for absorption in the intestine.

The increase in rate and degree of absorption of quinine due to oral dilution with a large volume of water results in an enhancement of the toxic effects of the drug.

Table 2. The effect of oral dilution on plasma quinine concentrations

Time after drug administration (minutes)	Control Animals (mg./100 ml.)	Test Animals (mg./100 ml.)
15	2.9 (0.9-4.9)	6.9 (4.9-8.9)
60	6.0 (3.6-8.4)	10.3 (7.9-12.7)
120	7.2 (5.0-9.4)	11.7 (9.5-13.9)

Figure 2. The effect of oral dilution on plasma quinine concentration. Bracketed lines represent 95% confidence limits.

II C. ASPIRIN

Introduction:

Aspirin is one of the most widely used as well as misused drugs which accounts for 25% of all cases of ingested poisonings (Verhulst et al 1966). In the last seven years, it has accounted for 16.3% of the total cases reported in Arizona (Arizona Poisoning Control Information Center, unpublished data). Aspirin accounts for nearly one-third of those deaths due to poisons in children under five years of age (National Clearinghouse for Poison Control Centers Bulletin 1963).

Aspirin is considered to be readily absorbed from both the stomach and small intestine (Schanker 1962, Levy 1963, Martin 1964).

The symptoms of mild acute poisoning include nausea, vomiting, tinnitus, hyperpnea, fever, lethargy and mental confusion, and, if more severe, includes convulsions, coma, severe dehydration and respiratory failure (vonOettingen 1952, Cecil 1959, Done 1960, Cumming 1961, Finberg 1961, Dreisbach 1963, Davison and Mandel 1965, Done 1965, Woodbury 1965). The majority of these symptoms could not be observed in rats but plasma aspirin levels are easily determined.

Experimental:

Female Sprague-Dawley rats, weighing 170 to 260 grams, were fasted for 24 hours and divided into control and test groups of five animals. The animals were allowed free access to water except during the last hour prior to testing. Aspirin, 200 mg./Kg., as an aqueous

suspension,¹ was given by oral intubation in a volume of 2 ml./Kg.; one minute later the control animals were administered a small volume of water (1 ml./Kg.) by gavage and the test animals were administered a large volume of water (20 ml./Kg.). At 5, 15, and 60 minutes after drug treatment, a control and a test group of animals were anesthetized with ether and blood samples collected from the abdominal aorta. The plasma was analyzed for salicylate by the method of Trinder (1964) and described in Appendix C. At the 5-minute time period, the plasma samples were incubated in a waterbath at 37°C. for two hours to ensure that all of the aspirin was hydrolyzed to salicylic acid (Cotty et al 1965).²

Results:

The results of the aspirin study are presented in Table 3 and Figure 3. The plasma level of aspirin in test animals did not differ significantly from those of the corresponding control animals during the 5-, 15- and 6- minute period ($p > 0.05$).

Discussion:

Oral dilution with water is presumed to delay absorption of noxious substances from the gastrointestinal tract (American Red Cross 1957, Dreisbach 1963). However, the results of the aspirin study

1. The aspirin was triturated in a mortar and sifted through a 100-mesh sieve in order to provide a more uniform suspension and to reduce variability in absorption (Winter, Risley and Nuss 1962).

2. Preliminary studies in this laboratory demonstrated that aspirin was completely hydrolyzed to salicylic acid in plasma collected 15 and 60 minutes after drug treatment; hence, plasma was not incubated at these two time periods.

Table 3. The effect of oral dilution on plasma salicylate concentration

Time after drug administration (minutes)	Control animals (mg./100 ml.)	Test Animals (mg./100 ml.)
5	9.8 (4.6-15.0)	14.8 (9.6-20.0)
15	27.2 (22.3-32.1)	25.8 (20.9-30.7)
60	32.3 (23.4-41.4)	32.8 (23.8-41.7)

Figure 3. The effect of oral dilution on plasma aspirin concentration. Bracketed lines represent 95% confidence limits.

indicate that oral dilution with large volumes of water has no significant influence on the rate of absorption of aspirin.

Aspirin is readily absorbed from the stomach and small intestine (Schanker 1962, Levy 1963, Martin 1964). Martin (1964) states that absorption is very rapid and complete. In the present study, since the plasma salicylate concentration of the test rats is no higher than that of the control rats, it could be postulated that aspirin is absorbed so rapidly and completely that oral dilution has no significant effect on the gastrointestinal absorption of this drug.

A 10% suspension of aspirin was prepared in 0.1% Tween 80, a surface active agent, in an attempt to prepare a more uniform preparation. As a result, in both control and test animals, blood concentrations were found at 15 minutes which remained at that constant level for 2 hours. Due to the marked influence of Tween 80 on the absorption of the aspirin, the use of this suspending agent was discontinued. Other investigators have reported that surface active agents will hasten absorption (Hagen 1959).

III. GENERAL DISCUSSION

Oral dilution with water is widely recommended as a first aid treatment for ingested poisons because it is presumed to delay absorption of noxious substances from the gastrointestinal tract (American Red Cross 1957, Dreisbach 1963). However, the results of the present investigation indicate that oral dilution with large volumes of water increases the rate and degree of gastrointestinal absorption of pentobarbital and quinine, although it has no significant effect on the absorption of aspirin.

Some factors which influence the absorption of drugs from the gastrointestinal tract include: (1) degree of ionization of the drug, (2) lipid solubility of the nonionized form of the drug, (3) rate of gastric emptying time, (4) concentration of the drug in the gastrointestinal tract, (5) solubility of the drug in the digestive system, and (6) the size of the area over which the drug is spread (Schanker et al 1957, Schanker et al 1958, Hogben et al 1959, Schanker 1962, Wilson 1962, Schanker 1963, Goth 1964, Brodie 1964, Truitt and Morgan 1964). Oral dilution with a large volume of water would tend to affect factors 3, 4, and 6. The fluid administered to the test animals hastens gastric emptying; indeed, it is possible that most of the drug is forced from the stomach into the intestine. This factor in itself may enhance, retard, or have no effect on gastrointestinal absorption, depending upon the physico-chemical nature of the administered agent and depending on the part or parts of the digestive tract involved in the absorption of

that chemical. The large volume of water also reduces the concentration of the drug in the gastrointestinal tract; this factor would tend to reduce the rate of drug absorption. However, oral dilution causes a marked increase in surface area over which absorption may take place; this factor undoubtedly exerts a more significant effect on gastrointestinal absorption than does the factor of decreased concentration of the drug.

Dreisbach (1963), who has recommended oral dilution as a first aid treatment in poisoning, warns that the volume of fluid given should not exceed the capacity of the stomach, otherwise the noxious material may be forced into the intestine and absorption would be increased. However, due to the increased surface area for absorption in the stomach following oral dilution, absorption is likely to be enhanced even in the absence of gastric emptying.

Although the present investigation involves only three chemical agents, it appears logical to conclude that oral dilution would generally be ineffective in retarding the gastrointestinal absorption of ingested chemicals. The act of dilution with water cannot occur without a concomitant increase in volume and a consequent increase in surface area from which absorption of a chemical can take place.

IV. SUMMARY AND CONCLUSIONS

Results of this investigation indicate that oral dilution with large volumes of water in the treatment of poisoning from pentobarbital or quinine will increase the rate and amount of the drug absorbed and thus intensify its toxic effects although it has no significant effect on the absorption of aspirin.

In view of the possibility that oral dilution may enhance gastrointestinal absorption of chemicals, it is suggested that this procedure not be employed as a first aid treatment for ingested systemic poisons.

APPENDIX A

Pentobarbital blood concentrations were analyzed by the method of Goldbaum (1948) as modified in this laboratory (Picchioni et al 1966). Five milliliters of blood were extracted by gentle shaking with 30 ml. of chloroform AR for three minutes to remove the pentobarbital from the blood. Following filtration through dry filter paper, a 20 ml. aliquot was then shaken with 5 ml. of 0.45 N. sodium hydroxide for three minutes. Three milliliters of the aqueous alkaline extract were placed in a quartz cuvette and read in a Beckman DU spectrophotometer at 254 millimicrons. The standard curve was prepared by adding various concentrations of pentobarbital sodium to rat blood and extracting as described above.

APPENDIX B

Quinine was assayed by the fluorometric method of Brodie and Udenfriend (1943). After 1 ml. of plasma was added to 39 ml. of water and 10 ml. of 20% metaphosphoric acid AR, the mixture was shaken vigorously to insure complete precipitation of plasma proteins. After 15 minutes, the mixture was centrifuged for 10 minutes. Two milliliters of the clear supernatant were placed in a cuvette and read in an Aminco-Bowman spectrophotofluorometer at an activation wavelength of 360 millimicrons and a fluorescent wavelength of 450 millimicrons. Standard high and low reference solutions were made by adding 0.5 ml. of a standard solution containing 1 or 2 mg. of quinine per liter, respectively, to 10 ml. of quinine-free plasma filtrate. The blank consisted of quinine-free plasma filtrate. The concentration of each sample was computed from the following formula:

$$\begin{array}{l} \text{Concentration} \\ \text{of sample} \\ \text{(mg./liter)} \end{array} = \begin{array}{l} \text{concentration} \\ \text{of low standard} \\ \text{(mg./liter)} \end{array} \times \frac{\begin{array}{l} \text{(concentration} \\ \text{of low standard} \\ \text{Difference between high} \\ \text{and low standards} \end{array} \begin{array}{l} \text{sample} \\ \text{x reading} \end{array})}{\text{Difference between high}} \times 50$$

APPENDIX C

Aspirin was analyzed by the method of Trinder (1954). One milliliter of plasma was added to 5 ml. of reagent solution¹ and shaken to assure complete precipitation of plasma proteins. The mixture was then centrifuged for 10 minutes and 3 ml. of the clear supernatant was placed in a quartz cuvette and read in a Beckman DU spectrophotometer at a wavelength of 540 millimicrons. The plasma concentration was then determined from a standard curve; the standards consisted of 1 ml. of various concentrations of salicylic acid solution added to 5 ml. portions of the reagent.

1. Reagent color solution composed of 4 grams ferric nitrate, 4 grams mercuric chloride and 12 ml. N hydrochloric acid per 100 ml. of solution.

REFERENCES

- Adams, William C.. 1961. Emetics in Accidental Poisoning. *Pediat. Clin. N. Amer.* 8:351-2.
- American National Red Cross. 1957. "First Aid Textbook." 4th ed., 19th printing, Doubleday, Garden City, N.Y. pp. 47-54.
- Arizona Poisoning Control Information Center, unpublished data.
- Becker, David, J., M. Sierra and F. Wasserman. 1963. Some Considerations in Poisoning with quinine & related compounds. *Milit. Med.* 128:1132-4.
- Brodie, Bernard B. 1964. Physico-Chemical Factors in Drug Absorption. In T. B. Binns (ed.). "Absorption and Distribution of Drugs." E. & S. Livingston Ltd. Edinburgh and London. pp. 16-48.
- Brodie, Bernard B. and S. Udenfriend. 1943. The Estimation of Quinine in human plasma with a note on the estimation of quinidine. *J. Pharmacol. Exp. Therap.* 78:154-158.
- Cann, Howard, D.S. Neyman and H.L. Verhulst. 1958. "Control of Accidental Poisoning--A Progress Report." *JAMA* 168:717-724.
- Cecil, Russell L. and R. F. Loeb. 1959. "A Textbook of Medicine." 10th ed. W. B. Saunders Co., Philadelphia, Pa. Vol. 1. pp. 508-9.
- Cotty, V., F. Zurzola, T. Beezley and A. Rodgers. 1965. Blood Levels of Aspirin Following the Ingestion of Commercial Aspirin-containing Tablets by Humans. *J. Pharm. Sci.* 54:868-870.
- Cumming, Gordon. 1961. "The Management of Acute Poisoning." Charles Thomas. Springfield, Ill. pp. 54-97.
- Davison, Clarke and H. G. Mandel. 1965. Nonnarcotic Analgesics and Antipyretics I. Salicylates. In Joseph DiPalma (ed.). "Drill's Pharmacology in Medicine." 3rd ed. McGraw-Hill, New York, N.Y. pp. 286-304.
- Done, Alan K. 1960. Salicylate Intoxication: Significance of Measurements of Salicylate in blood in cases of Acute Ingestion. *Pediatrics* 26:800.
- Done, Alan K. 1965. Salicylate Poisoning. *JAMA* 192:770-772.

- Dreisbach, Robert H. 1963. "Handbook of Poisoning, Diagnosis and Treatment." 4th ed. Lange Medical Publications, Los Altos, Calif. pp. 3,200,219,287.
- Ferguson, Hugh C. 1962. Dilution of Dose and Acute Oral Toxicity. Toxicol. Appl. Pharmacol. 4:759-762.
- Finberg, L. 1961. Clinical Aspects of Salicylate Poisoning in Children. Quart. Review of Pediatrics. 16:43-9.
- Flint, T.J. 1964. "Emergency Treatment and Management," 3rd ed. Saunders, Philadelphia, Pa. p. 411.
- Goldbaum, Leo R. 1948. An Ultraviolet Spectrophotometric Procedure for the Determination of Barbiturates. J. Pharmacol. Exp. Therap. 94:68-75.
- Goth, Andres. 1964. "Medical Pharmacology Principles and Concepts." 2nd ed. C. V. Mosby Co., St. Louis, Mo. pp. 21-25.
- Hagen, E. C. 1959. Acute Toxicity. In "Appraisal of the Safety of Chemicals in Food and Cosmetics." The Editorial Committee (ed.), Association of Food and Drug Officials of United States. p. 18.
- Hillman, Elizabeth and E. R. Harpur. 1961. Hazards to Health. Quinine poisoning. New Engl. J. Med. 164:138-9.
- Hogben, C. Adrian M., D. J. Tocco, B. B. Brodie, and L. S. Schanker. 1959. On the Mechanism of Intestinal Absorption of Drugs. J. Pharmacol. Exp. Therap. 125:275-282.
- Jacobziner, Harold. 1962. Poisonings. In L.E. Holt, Jr., R. McIntosh and H. L. Barnett (ed.). "Pediatrics." 13th ed., Appleton-Century-Crofts, New York, N.Y., pp. 1315-1322.
- Levy, Gerhard. 1963. In A.St.J. Dixon, B.K. Martin, M.J.H. Smith, and P.H.N. Wood (eds.). "Salicylates: An International Symposium." J & A. Churchill Ltd., London. p. 17.
- Martin, B.K. 1964. The absorption and Distribution of Salicylates. In T.B. Binns (ed.), "Absorption and Distribution of Drugs." E. & S. Livingston Ltd., Edinburgh & London. pp. 165-172.
- Maynert, Everett W. 1965. Sedatives and Hypnotics II. Barbiturates. In Joseph R. DiPalma (ed.). "Drill's Pharmacology in Medicine." 3rd ed. McGraw-Hill, New York, N.Y. pp. 188-207.
- National Clearinghouse for Poison Control Centers Bulletin. 1963. Poisoning Report Data for Children under 5 years of age. September-October 1963.

- Picchioni, Albert L., L. Chin, H. L. Verhulst, and B. Dieterle. 1966. Activated Charcoal vs. "Universal Antidote" as an Antidote for Poisons. *Toxicol. Appl. Pharmacol.* In press.
- Price, Henry L. and R. D. Dripps. 1965. Barbiturates. In Louis S. Goodman and A. Gilman (ed.). "The Pharmacological Basis of Therapeutics." 3rd ed. Macmillan, New York, N.Y. pp. 100-126.
- Rollo, Ian M. 1965. Drugs Used in the Chemotherapy of Malaria. In Louis S. Goodman and A. Gilman (ed.). "The Pharmacological Basis of Therapeutics." 3rd ed. Macmillan, New York, N.Y. pp. 1105-1113.
- Schanker, Lewis S. 1962. Passage of Drugs across Body Membranes. *Pharmacol. Rev.* 14:501-530.
- Schanker, Lewis S. 1963. Passage of Drugs across the Gastrointestinal Epithelium. In C.A.M. Hogben and P. Lindgren (ed.). "Drugs and Membranes." Pergamon Press, New York, N.Y. pp. 121-130.
- Schanker, Lewis S., D. J. Tocco, B. B. Brodie and C.A.M. Hogben. 1958. Absorption of Drugs from the Rat Small Intestine. *J. Pharmacol. Exp. Therap.* 123:81-88.
- Thienes, C. H. and T. Haley. 1964. "Clinical Toxicology." 4th ed. Lea & Febiger, Philadelphia, Pa. pp. 93-100.
- Trinder, P. 1954. Rapid Determination of Salicylates in Biological Fluids. *Biochem J.* 57:301-303.
- Truitt, Edward B., Jr. and A.M. Morgan. 1964. Gastrointestinal Factors in Aspirin Absorption. *J. Pharm. Sci.* 53:129-34.
- Verhulst, Henry L., J.J. Crotty and G. Maisel. 1966. The Pharmacist in Poison Prevention. *JAPhA* NS6:17-19.
- vonOettingen, W. F. 1952. "Poisoning A Guide to Clinical Diagnosis and Treatment." Paul B. Hoeber, Inc., New York, N.Y. pp. 268-269.
- Wilson, T. Hastings. 1962. "Intestinal Absorption." W.B. Saunders Co., Philadelphia, Pa. p. 46, 244-245.
- Winter, Charles, E.A. Risley and G. W. Nuss. 1962. Carrageenin-Induced Edema in Hind Paw of the Rat as an Assay for Antiinflammatory Drugs. *Proc. Soc. Exp. Biol. Med.* 111:544-547.
- Woodbury, Dixon M. 1965. Analgesics & Antipyretics. In Louis S. Goodman and A. Gilman (ed.). "The Pharmacological Basis of Therapeutics." 3rd ed. Macmillan, New York, N.Y. pp. 312-330.