(15) K. Nakamura and Y. Masuda, *Arch. Int. Pharmacodyn.*, **162,** 255(1966).
(16) H. M. Swenson, *J. Dent. Res.*, **33,** 468(1954).
(17) W. G. Shafer, *ibid.*, **27,** 768(1948).
(18) W. A. Dill, A. Kazenko, L. M. Wolf, and A. J. Glazko, *J. Pharmacol. Exp. Ther.*, **118,** 270(1956).
(19) T. Chang and A. J. Glazko, *J. Lab. Clin. Med.*, **75,** 145 (1970).
(20) G. J. Conard, C. O. Haavik, and K. F. Finger, *Pharmacologist*, **11,** 273(1969).
(21) O. H. Lowry, N. J. Rosebrough, A. L. Farr, and R. J. Randall, *J. Biol. Chem.*, **193,** 265(1951).
(22) K. Eik-Nes, J. A. Schellman, R. Lumry, and L. T. Samuels, *J. Biol. Chem.*, **206,** 411(1954).
(23) P. L. Altman and D. S. Dittmer, "Blood and Other Body Fluids," Biological Handbooks, Federation of American Societies for Experimental Biology, Washington, D. C., 1961, p. 307.
(24) A. Goldstein, *Pharmacol. Rev.*, **1,** 102(1949).
(25) J. T. Edsall and J. Wyman, "Biophysical Chemistry," vol. 1, Academic, New York, N. Y., 1958, p. 591.
(26) J. J. Burns, R. K. Rose, T. Chenkin, A. Goldman, A. Schulert, and B. B. Brodie, *J. Pharmacol. Exp. Ther.*, **109,** 346 (1953).
(27) M. C. Meyer and D. E. Guttman, *J. Pharm. Sci.*, **57,** 895 (1968).

ACKNOWLEDGMENTS AND ADDRESSES

Received January 15, 1971, from the *American Dental Association, Research Institute, Chicago, IL 60611*

Accepted for publication June 18, 1971.

Supported in part by N.I.D.R. Training Grant DE 171 and by the American Dental Association.

The authors are indebted to Miss Judy Osborn and Mr. John Edwards for technical assistance; to Dr. Anthony J. Glazko, Parke, Davis and Co., for supplying the hydantoin derivatives used in these studies; and to Dr. Gerard Casey, American Dental Association, for drawing human blood samples.

* To whom reprint requests should be addressed.

† Present address: School of Pharmacy, University of Wisconsin, Madison, WI 53706

‡ Present address: College of Pharmacy, University of Florida, Gainesville, FL 32603

Effects of Dietary Components on GI Absorption of Acetaminophen Tablets in Man

JAMES M. JAFFE, JOHN L. COLAIZZI*, and HERBERT BARRY, III†

Abstract □ Various high carbohydrate, high protein, and high lipid test meals were administered concurrently with acetaminophen tablets to human subjects to study the effects of foods on GI absorption of this drug. Balanced test meals and a fasting condition were also employed. An indication of the rate and extent of drug absorption was obtained by measuring urinary excretion at 1.5-hr. intervals over a 9-hr. period. The initial rate of excretion of acetaminophen and its metabolites was significantly reduced with a majority of the carbohydrate test meals. High protein, high lipid, or balanced meals appeared to have no statistically significant effect, while the fasting condition showed only a trend toward initially higher excretion values. The cumulative amounts of total acetaminophen and metabolites excreted in the urine at the end of 9 hr. showed little difference among test meals. The apparent inhibition of acetaminophen absorption by carbohydrate test meals could be partially attributed to an interaction with pectin in some cases.

Keyphrases □ Absorption kinetics, GI—acetaminophen tablets, effect of foods, man □ Acetaminophen tablets—effect of foods on GI absorption, man □ Dietary considerations—GI absorption of acetaminophen tablets in man □ Foods—effect of high carbohydrate, high protein, high lipid test meals on GI absorption of acetaminophen tablets, man

It is generally recognized that administration of drugs by the oral route a short time before or after a meal may alter absorption of the drug from the GI tract. However, few definitive studies have correlated specific dietary components with effects on drug absorption. Generally, meals have been reported to retard absorption. Wood (1) indicated that with five different commercial aspirin preparations tested in humans, half-lives of absorption were more than doubled by the nonfasting condition. Hirsch and Finland (2) demonstrated that similar doses of erythromycin stearate and erythromycin propionate administered orally after breakfast resulted in significantly lowered blood levels when compared with equal doses given before breakfast. In the same study, however, blood levels achieved with orally administered triacetyloleandomycin did not vary significantly when given either before or after breakfast.

Peterson and Finland (3) showed that sulfadiazine administered orally after the morning meal was absorbed more slowly, but more completely, than when administered to fasting subjects. Kirby *et al.* (4) and Rosenblatt *et al.* (5) showed that foods, especially those containing significant amounts of divalent metal ions, can inhibit absorption of tetracyclines, at least partially by a chelation mechanism. Reduction of absorption efficiency by food was also shown for orally administered lincomycin (6) and penicillin (7).

Contrary to these studies, others demonstrated that a meal preceding administration of a drug may enhance its absorption from the GI tract. Levy and Jusko showed that absorption of riboflavin (8) and riboflavin-5′-phosphate (9) was enhanced when administered orally after a standard breakfast of cornflakes and milk, and they attributed these effects to decreased intestinal transit rates. Crounse (10) demonstrated that the absorption of orally administered griseofulvin was doubled when given after a high lipid breakfast (consisting of bacon, eggs, cream, and butter) compared with high protein or high carbohydrate meals or even compared with the fasting state. More recently, Kabasakalian *et al.* (11) indicated that a high fat meal followed by griseofulvin administration at breakfast increased drug absorption,

Table I—Summary of Components Utilized in Test Meal Series I

Component	Food Used	Amount of Food Used, g.	Grams of Each Component in Amount of Food Used[a] C	P	L	Percent Daily Requirement[a] C	P	L
High protein	Tuna	178.0	0	50.0	1.4	0	52.6	1.3
High lipid	Pecans	75.3	9.5	6.9	55.0	3.2	7.3	52.4
High carbohydrate	Jelly	115.4	75.0	0.2	0	25.4	0.2	0
	Crackers	105.6	75.0	9.7	12.5	25.4	10.2	11.9

[a] C = carbohydrate, P = protein, and L = lipid.

Table II—Summary of Components Utilized in Test Meal Series II

Component	Food Used	Amount of Food Used, g.	Grams of Each Component in Amount of Food Used[a] C	P	L	Percent Daily Requirement[a] C	P	L
High protein	Turkey	152.0	0	50.0	5.9	0	52.6	11.9
High lipid	Butter	61.1	0.2	0.4	55.0	0.07	0.4	52.4
	Bread	23.0	11.2	11.3	0.54	3.8	2.3	0.5
High carbohydrate	Dates	199.0	150.0	4.4	1.2	50.8	4.6	1.2

[a] C = carbohydrate, P = protein, and L = lipid.

Table III—Summary of Components Utilized in Test Meal Series III

Component	Food Used	Amount of Food Used, g.	Grams of Each Component in Amount of Food Used[a] C	P	L	Percent Daily Requirement[a] C	P	L
High carbohydrate	Marshmallows	198.5	150	3.0	0	50.0	3.2	0
High carbohydrate	Crackers	211.2	150	19.4	25.0	50.8	20.4	23.8
High carbohydrate	Jelly	230.8	150	0.4	0	58.8	0.4	0

[a] C = carbohydrate, P = protein, and L = lipid.

but this effect was not found when the high fat meal followed by griseofulvin administration was at supper.

The present study reports the effects of some high carbohydrate, high protein, and high lipid test meals on the absorption of orally administered acetaminophen tablets in humans. The objective of this investigation was to determine whether effects of food on the absorption of this drug are specific with respect to the particular dietary component.

EXPERIMENTAL

Subjects—The subjects employed in this study were normal, adult, healthy, male Caucasians whose ages ranged from 20 to 31 years (average age 25 years) and whose weights ranged from 59 to 86 kg. (average weight 76 kg.).

Test Meals—The food given as test meals in Series I, II, and III consisted of one-half of the normal daily requirement for each component needed by an average 25-year-old male (12). For the balanced meal, each of the three components was one-third of the high component test meal. This information is summarized in Tables I–III. The pectin test conditions employed (Series IV) were based on the 0.4% of pectin contained in grape jelly[1] used in Series I. For comparison, a higher pectin test was also employed containing 10 times the amount of pectin (4%) present in the other pectin test. The pectin was administered as a jelly prepared by dispersing it in the 270 ml. of water which the subjects normally ingested at the initial time period. A major consideration in the selection of the specific foods necessary to provide the required components in Series I, II, and III was the relationship of that component to other components contained in the same food. To be considered acceptable, a food high in one component (*e.g.*, carbohydrate) could not contain any more than 20% of another component (protein or lipid). Another consideration was that the food be palatable with a minimum of discomfort for the subjects ingesting it.

Procedure for Subjects—The experimental subjects were required to fast after the evening meal prior to the morning that the test meal was to be administered. However, they were permitted to take tea, coffee, soda, or water. They were also asked to get a normal night's sleep. Upon arriving at the laboratory, the subjects ingested the test meal with 270 ml. of water. The time required for consuming the meals was approximately 10 min. Immediately upon completion of the meal, each subject took one 325-mg. acetaminophen tablet[2]. The subjects were then required to provide a total void every 1.5 hr. for a total of 9 hr. (six voids). Each participant was also required to drink 180 ml. of water after each void to assure an adequate volume of urine.

The subjects were instructed to refrain from eating or drinking food or beverage of any kind (except the specified amounts of water) for 5 hr. after administration of the test meal and drug. After this time, the subjects were permitted to resume their normal diets. The subjects repeated this sequence each week until all test meals of the series were taken.

Sequence of Tests—In each of the four test series, a group of subjects was tested with each of the different test meals or test conditions in the series, with a usual and minimal interval of 1 week between successive tests. Different subjects were assigned the test meals or conditions in different sequences in order to eliminate possible sequential effects. The series of tests were conducted with an interval of 1 month between Series I and II and less than 1 month between Series II and III. The interval between Series III and IV was about 10 months, and the entire testing procedure was completed within a span of 1.5 years.

Five subjects were common to each of the first two test meal series, three additional subjects were tested in Series I only, and three in Series II only. Series III was tested with six subjects (four of whom had been previously tested in both Series I and II and two of whom had been previously tested in Series II only). Series IV also involved six subjects (three of whom had been previously tested in Series I, II, and III and one of whom had been previously tested in Series II and III only).

Analytical—The analytical technique utilized for the determination of acetaminophen in urine was based on a procedure employed by Ballard (13) and adapted from the method of Welch and Conney (14). The method involves the acid hydrolysis of acetamino-

[1] Welch Foods, Inc., Westfield, NY 17487

[2] Tylenol tablets, supplied by McNeil Laboratories, Inc., Fort Washington, PA 19034

Table IV—Cumulative Amount of Acetaminophen (Milligrams) Excreted at Each Time Interval for Series I, II, III, and IV

	Hours					
	1.5	3	4.5	6	7.5	9
Test Series I						
Carbohydrate	10.2	44.1	102.2	143.8	181.2	198.5
Protein	37.0	89.0	137.5	173.0	196.5	214.8
Lipid	35.4	89.8	138.6	178.7	207.5	226.9
Balanced	28.0	84.0	137.4	173.4	195.9	213.1
Fast	70.2	132.7	161.8	199.3	229.3	247.5
Test Series II						
Carbohydrate	11.8	49.4	105.9	154.1	189.2	209.4
Protein	14.7	54.5	99.4	130.9	155.4	173.9
Lipid	23.2	68.0	108.9	144.7	173.1	188.4
Balanced	25.8	75.2	118.8	149.7	168.4	180.2
Fast	30.8	79.6	131.6	165.3	195.2	214.1
Test Series III (All Carbohydrate)						
Crackers	16.3	59.0	112.1	150.0	179.0	201.0
Jelly	9.2	49.2	122.5	174.5	209.4	233.2
Marshmallows	28.7	81.7	149.4	195.5	224.6	247.7
Test Series IV						
Fast	26.8	55.6	92.4	121.7	144.8	160.6
Low pectin	27.5	72.8	117.9	142.8	166.0	183.1
High pectin	13.5	57.2	103.3	144.6	172.7	198.3

phen and its conjugates present in the urine to *p*-aminophenol. This compound was then coupled with phenol in the presence of hypochlorite to form an indophenol dye, the concentration of which could be determined spectrophotometrically.

Statistical Analysis of Data—The data were expressed in terms of milligrams acetaminophen excreted, both at each successive 90-min. interval after ingestion and cumulatively to the last collection at 9 hr. The statistical reliability of the differences among test meals and conditions, time intervals, and test series was tested by analysis of variance with the aid of a program (BMD 02V) used on the IBM. 7090 computer (15). The residual term consisted of the pooled interactions of subjects with each of the other variables and combinations of variables included in the analysis. Separate analyses were performed for the five subjects tested in both Series I and II, for the six additional subjects tested in one but not the other of these two series, for the six subjects tested in Series III, and for the six subjects tested in Series IV.

RESULTS

Table IV shows the mean cumulative excretion of acetaminophen at each 1.5-hr. interval for the different test series. Effects of particular test meals or conditions on the rate of excretion are indicated by the noncumulative amounts excreted at each time interval portrayed in the figures.

Figure 1 shows a comparison among three test conditions (carbohydrate, fasting, and balanced) for the five subjects tested in both Series I and II. The carbohydrate test conditions decreased the amount of acetaminophen excreted initially, followed by a compensatory increase at later time intervals. An analysis of variance on the five subjects who participated in Series I and II provided a test of the difference between the carbohydrate and the balanced test meal conditions, which is the most comparable condition. This analysis showed a reliable interaction between test meals and times ($F = 9.39$, $df = 5/80$, $p < 0.001$), signifying a different excretion–time profile for the two test meals. Use of the linear trend for the six time periods results in an even higher F value ($F = 24.24$, $df = 1/80$, $p < 0.001$). Figure 1 shows that the amount of excretion after the carbohydrate test meals tended to be depressed in the earlier time periods and elevated in the later ones. The lower excretion values with carbohydrates than with the balanced test meals were statistically reliable during the first 1.5 hr. ($F = 9.26$, $df = 1/12$, $p < 0.05$) and at the 3-hr. time period ($F = 7.08$, $df = 1/12$, $p < 0.05$), whereas carbohydrate was reliably higher at 4.5 hr. ($F = 5.70$, $df = 1/12$, $p < 0.05$) and at 6 hr. ($F = 8.28$, $df = 1/12$, $p < 0.05$).

The data in Table IV indicate very little difference in acetaminophen excretion values at each time interval among the protein, lipid, balanced, and fasting conditions. An analysis of variance applied to these four conditions, omitting carbohydrate, showed no statistically significant differences. Although Fig. 1 shows that the fasting conditions resulted in elevated levels throughout the entire span of the test, there was no reliable difference among the five test meal conditions in cumulative excretion at the end of 9 hr.

Since the results obtained with carbohydrate differed from those obtained with the other test conditions in Series I and II, three different carbohydrate test conditions were compared with each other in Series III. Figure 2 shows sizable differences among them in temporal pattern of acetaminophen excretion. The interaction between the three test foods and six time intervals was statistically reliable ($F = 2.55$, $df = 10/75$, $p < 0.05$). There was also a statistically significant difference among the three test foods at the 1.5-hr. interval ($F = 5.17$, $df = 1/10$, $p < 0.05$), the lowest amount of acetaminophen being excreted with the jelly and the highest with the marshmallows. The crackers resulted in intermediate scores. The values obtained for the jelly treatment corresponded rather closely to the 1.5-hr. interval obtained for earlier carbohydrate results (crackers and jelly in Series I and dates in Series II). However, as with the carbohydrate test meals in Series I and II, the jelly treat-

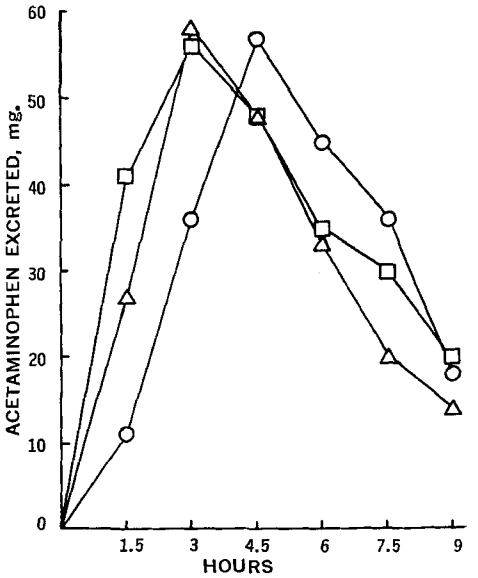

Figure 1—*Mean amount of acetaminophen excreted in the urine during each time interval for carbohydrate, balanced, and fasting conditions for the five subjects common to Series I and II (noncumulative). Key: □, fasting; △, balanced; and ○, carbohydrate.*

ment in Series III was only temporarily lower than the others. A compensatory increase for the jelly test meal began at 4.5 hr., at which time there was a reliable difference among the three treatments ($F = 7.43$, $df = 2/10$, $p < 0.05$). At the end of 9 hr., a statistically significant difference in cumulative acetaminophen excretion was found among the three carbohydrate test meals ($F = 6.22$, $df = 2/10$, $p < 0.05$). Table IV shows that the cumulative excretion was lowest with the crackers and highest with the marshmallows.

Since pectin was a component of the two carbohydrate test meals in Series I and II, and also of the jelly treatment in Series III which decreased acetaminophen excretion at the earliest time interval (1.5 hr.), low and high test conditions were compared with a fasting condition in Series IV. Figure 3 shows a comparison among the low pectin, high pectin, and fasting conditions. A statistically reliable interaction of test conditions with the linear function for the six time periods was found, comparing the high pectin test with the fasting condition ($F = 4.87$, $df = 1/50$, $p < 0.05$) and also with the low pectin test condition ($F = 7.28$, $df = 1/50$, $p < 0.01$). Figure 3 shows that after the high pectin treatment, the acetaminophen excretion was depressed in the initial time period and elevated in later time periods. Comparisons in particular time periods showed that the high pectin test condition differed reliably from the low pectin at 1.5 hr. ($F = 11.97$, $df = 1/5$, $p < 0.05$) and at 6 hr. ($F = 12.69$, $df = 1/5$, $p < 0.05$) and from the fasting condition at 6 hr. ($F = 10.73$, $df = 1/5$, $p < 0.05$).

DISCUSSION

The statistical analyses of the results of the four different phases of this study reveal that certain specific dietary components can significantly alter the absorption pattern of orally administered acetaminophen, while others result in only little or no difference from what is observed when the drug is administered in the fasting condition. These conclusions are based on the values obtained for the amounts of acetaminophen or its metabolites excreted in the urine of the subjects studied over 9 hr. The rate of urinary drug excretion is a function of the blood level of the drug and of its metabolites at any given time and, thus, serves as an indication of absorption.

The acetaminophen excretion averages obtained from Series I and II showed that there was significantly less total drug and metabolite excretion during the first 1.5-hr. interval with the high carbohydrate test meals, consisting of the crackers and jelly test meals (Series I) and also with the test meal of dates (Series II). In general, the other dietary components (protein and lipid) had little apparent effect on initial absorption of acetaminophen. Although the administration of all of the test meals resulted in lowered average values for the amount of total acetaminophen and metabolites excreted as compared with the fasted subjects, the trend was not entirely consistent.

In the third phase of the experiment, the comparison among three carbohydrate test meals showed that the ability to retard the initial absorption of acetaminophen does not appear to be common to all carbohydrate substances. The results of this portion of the study, in comparison with the findings obtained with the other series, showed that the absorption with marshmallows is more similar to the pattern found with the noncarbohydrate conditions. Both the jelly and the crackers test meals hindered absorption initially, jelly to the lesser extent, whereas the marshmallow test meal appeared to have little or no effect on acetaminophen absorption.

These findings indicate that certain carbohydrate substances (jelly, dates, and, to a lesser degree, crackers), when eaten in substantial amounts, initially inhibit the GI absorption of orally administered acetaminophen. The reduction of the amount of acetaminophen excreted averaged from 47 to 68% compared with lipid, protein, or balanced test meals during the first 1.5-hr. interval, and it averaged from approximately 22 to 41% over the initial 3-hr. period. Compared with the fasting condition, the reduction in the amount of acetaminophen excreted after the carbohydrate meals averaged from 60 to 76% over the first 1.5-hr. interval and from 33 to 53% over the initial 3-hr. period. These values indicate that the delayed absorption could probably be of clinical significance when analgesia is required.

A noteworthy fact is that the carbohydrate with the greatest inhibiting effect, jelly, contains a significant amount of pectin, whereas the carbohydrate with no inhibitory effect, marshmallows, contains little or no pectin. The carbohydrate test meals used in

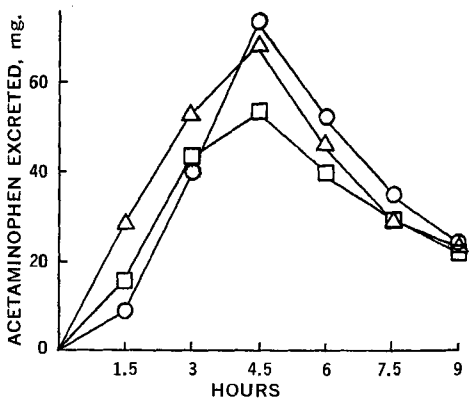

Figure 2—*Mean amount of acetaminophen excreted during each time interval for diets in Series III for the six subjects (noncumulative). Key: □, crackers; ○, jelly; and △, marshmallows.*

Series I (crackers and jelly) and probably also in Series II (dates) also contained pectin. A slightly greater inhibitory effect with Series I than with Series II might be due to a probably greater pectin content in the jelly–crackers test than in the test meal of dates. The crackers alone, in Series III, contain no pectin but differ from the other test meals in that they provide a large amount of starch, have minimal water content, are relatively bulky, absorb gastric fluids, and are not readily soluble in or miscible with the aqueous fluids of the GI tract. The marshmallows differ from the crackers in nearly all of these aspects.

This inhibitory effect of carbohydrate in Series I, II, and III persisted for 1–3 hr., followed in general by significantly higher acetaminophen excretion than with the other dietary conditions at these later time intervals. This trend also was seen in Series IV for the high pectin test but was slightly short of statistical significance at the 5% level. In general, the cumulative excretion values achieved with the subjects on jelly, dates, or jelly and crackers test meals were similar to the other test conditions at the intervals beyond 3 hr., although the actual amounts of drug excreted during the later intervals were greater with the carbohydrate test meals. The carbohydrates appear to cause merely a delay in absorption, extending it over a longer time period, rather than permanently inhibiting absorption.

In addition to the apparent lack of effect of marshmallows on acetaminophen absorption, the other noncarbohydrate conditions (protein, lipid, and balanced) cause only minimal and generally statistically insignificant effects on absorption as compared with the fasting condition. These findings are contrary to the common opinion that the presence of food in the GI tract generally reduces the rate or extent of drug absorption (16). A more realistic point of view, which has likewise been expressed as a generality, is that: "dietary

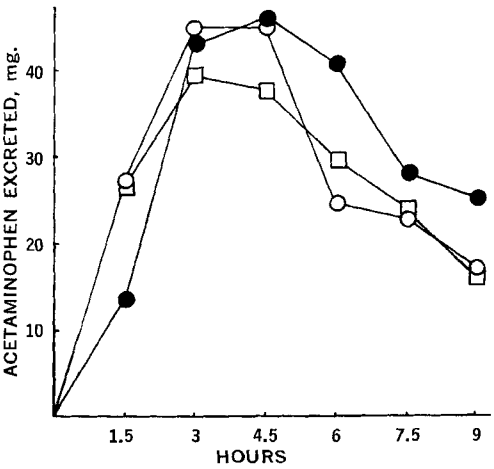

Figure 3—*Mean amount of acetaminophen excreted during each time interval for test conditions in Series IV for the six subjects (noncumulative). Key: □, fasting; ○, low pectin; and ●, high pectin.*

effects on drug absorption are quite variable and frequently depend on the physicochemical properties of the drug and the mechanism by which it is absorbed" (16). The results of the present study suggest that an inhibitory effect of food on drug absorption is limited to certain food components, to certain test conditions, or to certain types of subjects.

The present data give evidence that acetaminophen is capable of absorption from both the stomach and the intestine. This finding is in agreement with the work of Weikel and Lish (17) who found that, in rats, acetaminophen is absorbed from both the stomach and all portions of the small intestine and that it is relatively insensitive to changes in gastric emptying rates. The high carbohydrate test meals, which tended to retard acetaminophen absorption, would actually be expected to reduce the rate of gastric emptying less than the other test meals (18, 19), whereas the high lipid test meals, which markedly reduced the rate of gastric emptying, showed little or no tendency to retard acetaminophen absorption. Greater effects of the gastric emptying rate might be found with a drug such as aspirin, which is absorbed mainly from the stomach and the proximal small intestine (17).

The apparent depression of the initial absorption rates of acetaminophen by certain carbohydrates employed in this study cannot be explained by any effect of the monosaccharide or disaccharide sugar content alone, such as by competition for absorption sites or by viscosity effects, because this effect was not observed with the marshmallow high carbohydrate test meal. The depression of initial absorption rates found with all of the other high carbohydrate test meals could possibly be attributed to the pectin content in these substances. The presence of pectin in jelly and the likely presence of pectin or pectic substances in dates could reduce the absorption of acetaminophen by increasing viscosity and, thereby, possibly retarding both the dissolution rate of acetaminophen and the diffusion of dissolved acetaminophen throughout the gastric fluids and to the membrane absorptive sites. Pectin is known to act as an adsorbant and protectant in the GI tract and is used clinically as an antidiarrheal preparation for the purpose of adsorbing toxins, bacteria, and other noxious materials. Being polymeric in nature, pectin could also act as a complexing agent for drugs like acetaminophen in addition to possibly retarding absorption by adsorption. If the pectin content of jelly and dates is acting to retard absorption of acetaminophen by complexation or adsorption mechanisms, the process must be reversible since only the initial rate of absorption is retarded and not the ultimate amount of drug absorbed.

Series IV gave evidence that pectin alone can inhibit the rate of acetaminophen absorption. The high pectin test condition reduced the rate of absorption initially, as did the carbohydrate meals containing pectin in Series I–III. However, the amount of pectin contained in the jelly and dates test meals of Series I–III is probably more similar to the low pectin test condition of Series IV, which showed no reliable difference from the fasting condition. Thus, while the pectin content of these foodstuffs might have been a factor in retarding initial acetaminophen absorption, some other characteristics of the jelly and dates must have been involved.

Several factors might explain the reduction in initial acetaminophen absorption by crackers. The dry, bulky, and water-absorptive nature of crackers could decrease or delay absorption by decreasing the amount of biological fluid available in the GI tract and, thereby, reducing the dissolution rate of the drug, especially when administered as a solid dosage form (20). This could be a limiting factor in the absorption process since acetaminophen is considered to be only a very slightly soluble drug (21) for which dissolution would be rate limiting (22). Alteration of gastric emptying rate and intestinal transit time by bulk effects could also affect the absorption of acetaminophen since the bulk volume of the meal was greater for the crackers than for any of the other test meals. A tendency to complex with certain drugs was reported for starches, especially those drugs with amino or nitro groups (23). Since crackers are high in starch content and acetaminophen has an aminophenol structure, absorption might possibly be inhibited by a complex formation of this type.

REFERENCES

(1) J. H. Wood, *Lancet*, **2**, 212(1967).

(2) H. A. Hirsch and M. Finland, *Amer. J. Med. Sci.*, **237**, 693 (1959).

(3) O. L. Peterson and M. Finland, *ibid.*, **204**, 581(1942).

(4) W. M. M. Kirby, C. E. Roberts, and R. E. Burdich, *Antimicrob. Ag. Chemother.*, **1**, 286(1961).

(5) J. E. Rosenblatt, J. E. Barrett, J. L. Brodie, and W. M. M. Kirby, *ibid.*, **6**, 134(1966).

(6) J. G. Wagner, in "Determinants of Drug Activity," symposium, Philadelphia College of Pharmacy and Sciences, Nov. 14, 1968.

(7) J. O. Klein and M. Finland, *New Engl. J. Med.*, **269**, 1019 (1963).

(8) G. Levy and W. J. Jusko, *J. Pharm. Sci.*, **55**, 285(1966).

(9) W. J. Jusko and G. Levy, *ibid.*, **56**, 58(1967).

(10) R. R. Crounse, *J. Invest. Dermatol.*, **37**, 529(1961).

(11) P. Kabasakalian, M. Katz, B. Rosenkrantz, and E. Townley, *J. Pharm. Sci.*, **59**, 595(1970).

(12) Johns Hopkins Hospital, "Manual of Applied Nutrition," 5th ed., Johns Hopkins Press, Baltimore, Md., 1966, p. 14.

(13) B. E. Ballard, "Teaching Biopharmaceutics at the University of California: Laboratory Exercise in Pharmacokinetics—*In Vivo* Evaluation of Acetaminophen in Solution Taken before a Meal," presented at the American Association of Colleges of Pharmacy Teachers' Seminar on Pharmacy, West Virginia University, Morgantown, W. Va., June 1968.

(14) R. M. Welch and A. H. Conney, *Clin. Chem.*, **11**, 1064 (1965).

(15) "BMD Biomedical Computer Programs," 2nd ed., W. J. Dixon, Ed., University of California Press, Berkeley and Los Angeles, Calif., 1967.

(16) M. Gibaldi, in "The Theory and Practice of Industrial Pharmacy," L. Lachman, H. A. Lieberman, and J. L. Kanig, Eds., Lea & Febiger, Philadelphia, Pa., 1970, p. 242.

(17) J. H. Weikel, Jr., and P. M. Lish, *Arch. Int. Pharmacodyn. Ther.*, **119**, 398(1969).

(18) W. J. Bruback, *Ciba Clin. Symp.*, **11**, 3(1959).

(19) H. W. Davenport, "Physiology of the Digestive Tract," Year Book Medical Publishers, Chicago, Ill., 1962, p. 155.

(20) T. R. Bates and M. Gibaldi, in "Current Concepts in the Pharmaceutical Sciences: Biopharmaceutics," J. Swarbrick, Ed., Lea & Febiger, Philadelphia, Pa., 1970, p. 78.

(21) "The Merck Index," 8th ed., Merck and Co., Rahway, N. J., 1968, p. 5.

(22) A. H. Goldberg, M. Gibaldi, and J. L. Kanig, *J. Pharm. Sci.*, **55**, 482(1966).

(23) Z. Mansour and E. P. Guth, *ibid.*, **57**, 404(1968).

ACKNOWLEDGMENTS AND ADDRESSES

Received March 22, 1971, from the *Department of Pharmaceutics, University of Pittsburgh, Pittsburgh, PA 15213*

Accepted for publication July 8, 1971.

Presented to the Basic Pharmaceutics Section, APhA Academy of Pharmaceutical Sciences, San Francisco meeting, March 1971.

Supported in part by Grant 5-S01-RR-05455-09 (General Research Support Grant) from the National Institutes of Health, U. S. Public Health Service, Bethesda, Md.

* To whom inquiries should be addressed.

† Supported by a Public Health Service Research Scientist Development Award (K2-MH-5921) from the National Institute of Mental Health.