single extract. Effective use has been made of several reagents, however, such as: (*a*) a 0.1 *M* solution of cerium sulfate in water, (*b*) saturated methanol solution of aluminum sulfate, and (*c*) saturated water solution of sodium borate.

The common alkaloidal, sugar, and protein color producing reagents may also be employed. Work is in progress on the tabulation of extracts with corresponding spray reagents and will be described in a subsequent communication.

REFERENCES

(1) Lederer, E., and Lederer, M., "Chromatography," 2nd ed., Elsevier Publishing Co., New York, 1960.

(2) Consden, R., Gordon, A. H., and Martin, A. J. P., *Biochem. J.*, **38**, 224(1944).

(3) Konig, P., *Actas y trabajos cong. peruano quim. 2nd Congr.* **1937**, 334.

(4) Kokoski, C. J., Kokoski, R. J., and Slama, F. J., THIS JOURNAL, **47**, 715(1958).

(5) Burchfield, H. P., Prill, E. A., and Fisher, D., *Am. Perfumer Aromat.*, **71**, 49, 52(1958).

(6) Stahl, W. H., Voelker, W. A., and Sullivan, J. H., *J. Assoc. Offic. Agr. Chemists*, **43**, 606(1960).

(7) "The National Formulary," 11th ed., J. B. Lippincott Co., Philadelphia, Pa., 1960, p. 308.

Effects of Buffered and Unbuffered Acetylsalicylic Acid upon the Gastric Acidity of Normal Human Subjects

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Acetylsalicylic acid in tablet form, in buffered tablets, and effervescent buffered solution, has been compared with regard to the effect upon gastric acidity and pH. Aspirin and buffered aspirin have little or no effect as compared to controls, whereas the effervescent preparation reduces free acidity and raises gastric pH significantly for 30 minutes. This elevation of gastric pH correlates well with the more rapid absorption and reduced gastric irritation which has been reported for various soluble and buffered forms of salicylates.

DISADVANTAGES of acetylsalicylic acid as an analgetic and antipyretic agent are low solubility, which delays absorption (1), and gastric irritation and bleeding which may result from the erosive action of the crystals of the drug (2), or possibly from its acidity (3), as well as a neurohumoral action (4). It has been shown by Alvarez and Summerskill (5) that there is a causal relationship between salicylate consumption and massive gastrointestinal hemorrhage associated with peptic ulcer. For these reasons, there are a number of proprietary preparations of acetylsalicylate available which are buffered so as to minimize these problems. Several investigators have noted that such buffered preparations are more rapidly absorbed (6, 7). There are also scattered reports that soluble preparations of acetylsalicylic acid or salicylic acid are less irritating and less prone to produce gastric hemorrhage (8, 9). The present investigations were designed to compare the effects of such buffered preparations upon free and total gastric acidity and gastric pH, as compared to unbuffered aspirin.

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† Deceased October 1960.

PROCEDURE

For the initial experiments, subjects were selected at random from available laboratory personnel and included six male and one female subject. They were fasted for 12 hours prior to the experiment and then given a test meal consisting of 50 ml. of cold 45% alcohol, to stimulate gastric secretion. Fifteen minutes after the test meal each subject swallowed a stomach tube, and 5 minutes later withdrew a zero-hour sample of 10 ml. of fluid. Immediately after removal of this control sample the drugs were administered. Over a period of 2 weeks each subject received each drug and performed one experiment where only water was administered (control). Effervescent aspirin[1] was administered dissolved in water, two tablets in 250 ml. of water; buffered aspirin[2] and aspirin[3] were taken whole, two tablets followed by 250 ml. of water. All doses were equivalent to 650 mg. of acetylsalicylic acid. Controls received 250 ml. of water only.

Ten-milliliter samples of gastric juice were removed 10, 20, 30, and 40 minutes after administration of the drugs. All samples were tested for pH using pHydrion paper; for free acid by titration with 0.01 *N* sodium hydroxide to a change in color with Töpfers reagent (pH 3.5); and for total acidity by titration to the end point of phenolphthalein (pH 8.4). Free and total acidity are reported in clinical units (milliliters of 0.1 *N* sodium hydroxide required to neutralize 100 ml. of gastric juice).

[1] Marketed as Alka-Seltzer by Miles Laboratories.
[2] Marketed as Bufferin by Bristol-Myers Co.
[3] Bayer Aspirin.

In view of the wide variability observed in these subjects' results, the experiments using aspirin and effervescent aspirin were repeated under more carefully controlled conditions and with more accurate procedures for measurement of pH and free and total acidity.

Some of the subjects in the first series of experiments had experienced a great deal of difficulty in swallowing the stomach tube. In order to eliminate the possibility of such trauma affecting the response to the test meal, 35 prospective subjects were tested as to their ability to swallow the stomach tube without difficulty. Twelve were selected as having little or no difficulty and were used in this series of experiments; these included ten male and two female subjects. The test meal was changed to one designed to give better stimulation and consisted of 50 ml. of 14% ethanol to which was added one-half teaspoonful of dry Cream of Wheat to provide mechanical stimulation. The general procedure used was the same except that the drugs were administered with only 150 ml. of water. The pH was measured using the Beckman Zeromatic pH meter. Free and total acidity were measured by titration with 0.01 *N* sodium hydroxide to pH of 3.5 and 8.4, respectively, as measured by the pH meter.

RESULTS

The subjects exhibited a widely varying and generally poor response to the test meal used. In spite of this, marked differences were obtained with the drugs tested (Table I). Effervescent aspirin caused an immediate elevation in gastric pH which reached a maximum of 2.2 pH units above the water control at 20 minutes, and decreased thereafter. A statistical analysis revealed that the gastric pH with the effervescent preparation was significantly higher at 10 and 20 minutes ($P < 0.05$ and < 0.001, respectively) than with the other three preparations. After 20 minutes no differences were seen. The other two salicylate preparations do not affect the pH significantly at any time, nor do they alter free acidity, as compared to the water control. The free acidity drops sharply after the administration of the effervescent drug, the difference being highly significant ($P < 0.01$) at 10, 20, and 30 minutes, and probably significant at 40 minutes ($P = 0.05$). Total acid levels were also compared by the analysis of variance technique, and no differences were found among the drugs.

The second series of experiments, employing a test meal of greater stimulatory capacity and selected subjects, was much more uniform. Effervescent aspirin again produced a marked elevation in pH as compared to aspirin (Table II, Fig. 1) and a marked drop in free acidity (Table II, Fig. 2). An analysis of variance was again performed, followed by comparisons at the individual times by the technique of Scheffe (10). The pH differences were highly significant through 30 minutes ($P < 0.001$) and probably significant at 40 minutes. Differences in free acidity were also significant at 10, 20, and 30 minutes ($P < 0.01$). Total acidities differed only at the 40-minute measurement at a low level of significance ($P < 0.05$).

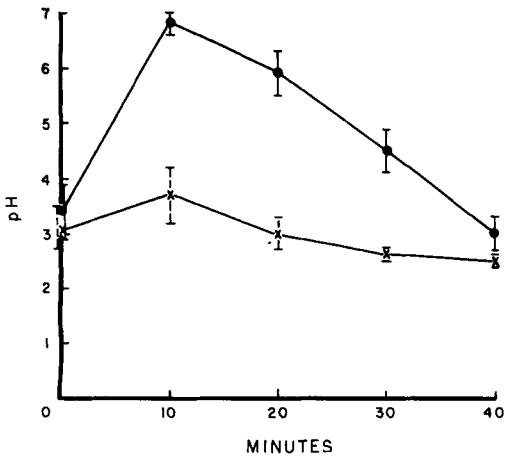

Fig. 1.—Comparison of the effects of 650 mg. of aspirin or effervescent aspirin upon the gastric pH of 12 normal subjects after a standard test meal. Vertical bars represent the standard error of the mean. ●, Effervescent aspirin; ×, aspirin.

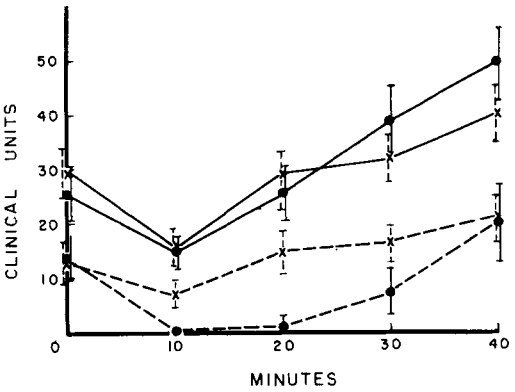

Fig. 2.—Comparison of the effects of 650 mg. of aspirin or effervescent aspirin upon the free and total gastric acidities of 12 normal subjects after a standard test meal. Vertical bars represent the standard error of the mean. ●, Effervescent aspirin; ×, aspirin; — total acidity; - -, free acidity.

DISCUSSION

The results as presented in the tables and figures indicate clearly that effervescent aspirin decreases the free gastric acidity and increases the pH for at least 30 minutes. In contrast, acetylsalicylic acid tablets and buffered aspirin increase the pH only slightly, and depress the acidity to a small degree. This latter effect is presumably due only to dilution of the gastric contents with the ingested water, since these effects did not differ from the controls. Rubin, Pelikan, and Kensler (11) measured intragastric pH levels after the administration of placebos, acetylsalicylic acid, and buffered aspirin, and noted an increase of 0.24 to 0.29 pH units in all cases, these differences not being statistically significant. It will be noted that the pH of those subjects ingesting acetylsalicylic acid tablets or buffered tablets never exceeded 3.7, falling to 2.6 by 40 minutes. This might be expected since at this dosage the buffered aspirin had a neutralization equivalent of only 5 meq. of hydrochloric acid (50 ml. of 0.1 *N* hydrochloric acid). Since the pKa of acetylsalicylate is

TABLE I.—EFFECT OF SEVERAL ASPIRIN PREPARATIONS UPON GASTRIC ACIDITY

Subject	Free Acid Clinical Units 0	10	20	30	40	Total Acid Clinical Units 0	10	20	30	40	pH 0	10	20	30	40
No Drug Administered															
A	23.0	12.0	48.5	63.5	53.5	32.5	15.5	52.5	71.5	53.5	2.1	2.4	1.6	1.4	1.4
B	10.0	22.5	35.5	34.0	39.5	21.5	32.5	50.0	45.0	53.5	2.8	1.7	1.4	1.4	1.4
C	0.0	2.5	24.0	52.5	0.0	6.0	5.5	36.0	61.5	9.5	5.5	4.0	1.4	1.5	4.0
D	0.0	0.0	0.0	0.0	0.0	3.0	1.0	4.0	4.0	8.0	5.5	5.5	5.5	5.0	4.8
E	5.0	5.0	6.0	35.0	34.0	12.0	10.0	3.0	43.0	41.0	3.5	3.0	1.7	1.4	1.7
F	0.0	2.5	8.0	24.0	42.5	9.5	12.5	16.5	36.0	50.0	5.5	4.0	2.4	2.0	1.5
G	0.0	1.0	4.5	7.5	14.5	7.0	4.5	8.0	13.0	18.5	4.0	3.0	3.0	2.5	2.0
Mean	5.45	6.50	18.05	30.80	26.15	13.10	11.65	24.30	39.15	33.45	4.13	3.37	2.43	2.17	2.40
S.E.	3.27	3.06	6.94	8.60	8.06	3.93	3.96	8.15	9.16	7.84	0.53	0.47	0.56	0.50	0.53
Aspirin Tablets															
A	22.0	13.5	37.5	65.0	63.0	33.0	17.0	43.5	76.0	70.0	1.7	1.7	1.4	1.4	1.4
B	0.0	4.5	18.0	27.0	29.5	6.0	11.0	33.5	39.5	33.0	5.0	3.7	2.4	1.8	1.4
C	5.0	2.5	3.5	2.0	8.5	18.5	9.0	15.0	28.0	34.0	2.8	3.0	3.6	3.0	2.8
D	8.0	4.0	2.5	0.0	0.0	23.0	5.5	13.5	5.0	4.0	2.0	2.8	3.8	5.0	5.5
E	0.0	0.0	4.0	8.0	49.0	3.0	5.0	7.5	18.0	59.5	7.5	5.0	3.8	2.8	1.5
F	0.0	4.0	33.5	61.0	72.0	3.5	16.0	40.5	75.0	81.0	5.5	3.0	1.7	1.4	1.4
G	0.0	5.0	9.0	28.5	40.5	11.0	13.0	14.5	36.0	45.5	3.8	3.5	2.5	1.8	1.5
Mean	5.0	4.8	15.50	27.35	32.35	19.0	10.95	24.00	39.65	46.70	4.04	3.24	2.74	2.46	2.21
S.E.	3.07	1.58	5.59	10.15	10.10	4.27	1.79	5.55	10.20	9.82	0.79	0.38	0.38	0.49	0.58
Buffered Aspirin Tablets															
A	10.0	6.0	23.0	34.5	44.0	17.5	1.2	34.0	41.0	56.0	2.0	2.4	1.8	1.4	1.4
B	0.0	0.0	23.0	36.5	17.0	4.5	5.5	38.5	51.5	39.5	7.5	6.0	1.8	1.8	2.4
C	4.5	0.0	7.0	23.0	33.5	8.0	5.5	12.5	36.0	41.0	3.0	4.0	3.0	1.7	1.4
D	8.0	4.5	18.0	30.0	38.0	30.5	10.0	25.0	48.0	61.0	2.1	2.8	1.7	1.4	1.4
E	13.0	10.0	11.5	11.5	6.0	23.0	16.5	16.7	17.0	12.5	2.4	2.4	2.4	2.1	3.0
F	0.0	9.5	23.5	43.5	49.5	1.5	16.0	31.0	43.5	61.0	5.5	2.8	1.7	1.4	1.4
G	0.0	2.0	0.0	12.0	28.0	5.5	8.0	8.0	22.0	41.5	4.0	3.5	4.0	3.0	2.5
Mean	5.05	4.55	15.15	27.30	30.55	14.95	10.50	23.55	37.0	44.65	3.78	3.41	2.34	1.83	1.93
S.E.	2.03	1.57	3.49	4.65	5.76	4.12	1.72	4.40	4.92	6.45	0.78	0.48	0.33	0.22	0.26
Effervescent Aspirin Tablets															
A	14.5	0.0	0.0	0.0	21.0	20.0	8.0	7.0	22.5	36.0	2.1	5.5	5.5	3.8	2.0
B	0.0	0.0	0.0	0.0	0.0	5.0	5.0	9.5	23.5	32.0	5.5	5.5	5.5	4.5	3.5
C	0.0	0.0	0.0	40.5	23.0	5.0	4.5	2.0	55.0	38.5	5.0	5.5	5.5	1.4	1.4
D	0.0	0.0	0.0	0.0	0.0	4.0	6.0	10.5	9.5	13.5	5.5	5.5	5.5	5.0	5.0
E	0.0	3.5	17.5	43.5	44.5	16.0	15.0	37.0	55.0	65.0	3.0	3.0	2.5	1.5	1.5
F	0.0	0.0	0.0	0.0	44.0	6.0	16.0	5.5	13.0	68.5	5.5	4.0	4.0	4.5	1.5
G	21.5	0.0	0.0	0.0	19.0	22.0	4.0	8.5	39.0	81.5	1.7	5.5	5.5	4.0	1.4
Mean	5.15	0.50	2.50	12.00	24.50	11.85	8.35	11.45	31.05	47.85	4.04	4.93	4.86	3.53	2.33
S.E.	3.41	0.50	2.50	7.75	8.47	2.61	1.91	4.40	7.11	9.12	0.65	0.38	0.45	0.50	0.53

TABLE II.—EFFECT OF ASPIRIN AND EFFERVESCENT ASPIRIN ON GASTRIC ACIDITY

Subject	Free Acid, Clinical Units					Total Acid, Clinical Units					pH				
	0	10	20	30	40	0	10	20	30	40	0	10	20	30	40
Aspirin Tablets															
A	10.0	0.0	18.9	20.0	17.3	20.5	7.3	35.5	42.3	32.8	2.6	3.8	2.5	2.6	2.3
B	19.6	8.2	16.6	27.3	32.8	38.2	16.4	37.3	45.5	66.3	2.3	2.8	2.5	2.2	2.5
C	3.6	7.5	2.8	14.1	12.7	15.9	15.9	16.6	25.0	30.0	2.8	2.8	3.2	2.5	2.5
D	25.5	10.9	15.9	8.2	18.7	44.6	20.5	34.8	23.7	37.8	2.3	2.5	2.5	2.8	2.3
E	0.0	0.0	0.0	0.0	10.0	12.7	6.4	19.6	10.5	26.4	4.0	3.6	3.5	3.4	2.6
F	34.1	16.4	32.3	23.2	53.0	52.8	30.0	50.0	36.4	74.2	2.8	2.4	2.2	2.2	2.0
G	8.2	3.2	8.6	12.7	10.5	30.9	9.1	13.2	25.0	29.6	2.7	2.9	2.7	2.5	2.6
H	7.7	0.0	2.7	10.0	12.7	25.9	2.3	15.9	27.8	34.9	2.8	7.1	3.1	2.6	2.7
K	3.6	2.3	19.6	3.6	10.5	24.6	13.4	30.5	16.8	24.6	3.0	3.2	2.3	2.9	2.6
L	6.4	8.2	10.9	16.8	18.7	29.6	20.7	26.4	35.0	34.6	2.9	2.8	2.7	2.6	2.5
M	0.0	0.0	0.0	5.9	4.6	2.3	2.0	4.8	22.3	23.2	7.2	7.9	6.4	2.7	2.8
O	40.9	29.2	45.5	46.4	44.6	55.0	41.9	60.7	71.4	69.6	2.1	2.2	2.0	2.1	2.2
Mean	13.3	7.2	14.5	15.7	20.5	29.4	15.5	28.8	31.8	40.3	3.12	3.65	2.97	2.59	2.48
S.E.	3.94	2.48	3.96	3.64	4.34	4.63	3.39	4.64	4.63	5.34	0.40	0.54	0.34	0.10	0.07
Effervescent Aspirin															
A	10.0	0.0	0.0	0.0	0.0	20.0	21.4	29.1	43.2	45.5	2.5	7.2	5.3	4.1	4.6
B	16.4	0.0	0.0	0.0	30.5	25.5	5.5	10.9	51.0	68.7	2.4	7.2	6.8	3.9	2.4
C	11.4	0.0	0.0	0.0	10.9	21.4	6.8	9.1	32.1	46.4	2.6	7.3	6.7	5.2	2.9
D	32.3	0.0	0.0	19.6	59.6	51.0	24.6	28.7	66.0	77.4	2.2	6.4	6.1	3.0	2.2
E	15.0	0.0	0.0	0.0	0.0	25.5	23.7	34.6	34.1	29.6	2.4	6.2	6.5	5.5	4.8
F	53.7	0.0	17.3	50.0	74.9	64.6	35.5	70.5	89.2	99.6	2.2	5.5	2.6	2.0	1.8
G	1.4	0.0	0.0	0.0	13.5	19.1	9.6	21.8	36.4	41.9	3.3	7.1	6.4	5.3	2.8
H	0.0	0.0	0.0	0.0	15.0	6.4	12.7	19.6	28.2	32.8	7.1	6.7	6.0	4.9	2.5
K	11.4	0.0	0.0	15.9	0.9	24.6	5.5	43.7	27.0	16.8	2.7	6.7	4.3	2.5	3.2
L	0.0	0.0	0.0	0.0	12.7	16.4	6.8	16.4	29.6	54.6	3.5	7.1	6.8	4.8	2.5
M	0.0	0.0	0.0	0.0	0.0	4.6	8.6	7.7	13.5	21.8	7.0	7.6	7.3	6.9	4.3
O	10.5	0.0	0.0	0.0	19.1	27.3	16.4	15.9	15.0	56.0	2.8	6.6	6.5	6.3	2.4
Mean	13.5	0.0	1.44	7.1	19.8	25.5	14.8	25.7	38.8	49.3	3.39	6.8	5.94	4.53	3.03
S.E.	4.89	0.0	1.44	4.37	7.00	4.09	2.78	5.15	6.2	6.92	0.51	0.16	0.38	0.43	0.29

3.49, this means that a large proportion of the drug is unionized and of relatively low solubility throughout the period of measurement. The solubility of the drug is about 6.6 Gm./L. at 37° at pH 3 in dilute hydrochloric acid, so that all of the 650 mg. could be in solution in the volume of water used. However, the local pH at the mucosal wall and the diffusion constants of solid acetylsalicylic acid as it goes into solution would modify the rate of solution. Edwards (1) made theoretical calculations concerning such factors, and Nelson and Schaldemose (12) confirmed these experimentally by showing that acetylsalicylic acid in aqueous solution was much more rapidly absorbed than a comparable amount in tablet form. In contrast, after the administration of effervescent aspirin, the pH remained above 4.5 up to 30 minutes so that the drug would be more than 90% in the ionized form throughout this period. The effervescent preparation contains about 10 times more buffer, equivalent to 48 meq. It will also be noted that this large amount is not reflected in the total acid titrations; in the second experiment at 40 minutes, the increase was only 0.9 meq./100 ml. of gastric juice. This must result from the relatively rapid passage of a large proportion of the buffered gastric juice into the intestine. Moreover, Bolton (13) has demonstrated that citrate enhances solubility of acetylsalicylic acid, so that in pH 4.5 sodium citrate, acetylsalicylate is soluble to the extent of 32.4 Gm./L. at 30°. Obviously, solubility is not a problem with this buffered preparation and probably accounts for its more rapid absorption, reaching a peak at 30 to 45 minutes (6, 7). The enhanced solubility may very well reduce the gastric irritation associated with plain aspirin. In a group of 103 patients, Alvarez and Summerskill (5) incriminated salicylates in over 40% of cases admitted for hematemesis and melena connected with peptic ulcer. Stubbe (8), in studying patients with rheumatoid arthritis, observed that about 70% of these patients and a control population gave positive benzidine tests for occult blood in the stool regardless of the amounts of aspirin ingested. Enteric coated aspirin gave positive results also, but when positive patients (on aspirin) were changed to sodium salicylate, the benzidine tests became negative. In recent work, Stubbe (14, unpublished) has shown that positive benzidine tests for occult blood occurring when patients were on aspirin became negative when the medication was changed to effervescent aspirin. Pierson, *et al.* (9), employing chromium-tagged red cells, made similar observations with calcium aspirin complex and choline salicylate. Muir and Cossar (2) have seen crystals of acetylsalicylate for as long as several hours after tablet administration. Davison and Guy (unpublished) observed more occult blood produced in pyloric pouch dogs at acid pH values after the administration of acetylsalicylate as opposed to neutral pH. It would appear, therefore, that the erosive properties of the crystalline form of acetylsalicylic acid may account for at least a part of its hemorrhagic properties.

Hurley (15, unpublished), using gastroscopic observations in dogs and substantiated by photographs, has evaluated the local effects of aspirin and soluble effervescent aspirin on the gastric mucosa over a 2-week period. Aspirin produced initial characteristic erosions of the mucosa with hemorrhage, which cleared after 5 days and remained so for the balance of the dosage period. Administration of soluble effervescent aspirin over the same period had no effect on the mucosa. If aspirin is administered following a previous period of effervescent aspirin, the characteristic erosion and hemorrhage occur which clears up after 1 week.

Winkelman (16) suggests that while aspirin and associated salicylates are incriminated in bleeding, with or without peptic ulcer, no proved effect has been demonstrated, but proposed that factors responsible for ulcer production, such as impaired mucosal resistance or increased acid-pepsin secretion, may enhance the development of acute ulceration from salicylate-induced gastritis in some patients.

As Brodie and Hogben (17) have pointed out, it is apparently the unionized form of the drug which is absorbed, and Davison and Guy (unpublished) have confirmed this in dogs with pyloric pouches. Consequently, the buffered forms of acetylsalicylic acid should be absorbed more slowly on the ionic basis but, apparently, the enhanced solubility and consequent distribution over the entire stomach wall, as well as the more rapid penetration into the intestine, overcome this deficiency. Acetylsalicylic acid can even be absorbed within the intestine despite apparently unfavorable pH since, according to Brodie and Hogben (17), the pH of the intestinal wall can be as low as 5.3.

REFERENCES

(1) Edwards, L. J., *Trans. Faraday Soc.*, **47,** 1191(1951).
(2) Muir, A., and Cossar, I. A., *Lancet*, **1,** 539(1959).
(3) Garrett, E. R., THIS JOURNAL, **48,** 676(1959).
(4) Levrat, M., and Lambert, R., *Am. J. Digestive Diseases*, **5,** 623(1960).
(5) Alvarez, A. S., and Summerskill, W. H. J., *Lancet*, **2,** 920(1958).
(6) Carlo, P. E., Cambosos, N. M.. Feeney, G. C., and Smith, P. K., THIS JOURNAL, **44,** 396(1955).
(7) Lester, D., Lolli, G., and Greenberg, L. A., *J. Pharmacol. Exptl. Therap.*, **87,** 329(1956).
(8) Stubbe, L. T. F. L., *Brit. Med. J.*, **1958,** 1062.
(9) Pierson, R. N., Holt, P. R., Watson, R. M., and Keating, R. P., *Am. J. Med.*, **31,** 259(1961).
(10) Scheffe, H., *Biometrika*, **1,** parts 1 and 2(1953).
(11) Rubin, R., Pelikan, E. W., and Kensler, C. J., *New Engl. J. Med.*, **261,** 1208(1959).
(12) Nelson, E., and Schaldemose, I., THIS JOURNAL, **48,** 489(1959).
(13) Bolton, S., *ibid.*, **49,** 237(1960).
(14) Stubbe, L. T. F. L., personal communication.
(15) Hurley, J. W., personal communication.
(16) Winkelman, E. I., *Univ. Mich. Med. Bull.*, **26,** 182 (1960).
(17) Brodie, B. B., and Hogben, C. A. M., *J. Pharm. and Pharmacol.*, **47,** 1191(1951).