TABLE I.—PRECISION AND ACCURACY ANALYSIS OF A SYNTHETIC APC MIXTURE

	Component	Composition by Synthesis, % by Wt.	Run 1	Run 2	Run 3	Run 4	Mean	Av. Deviation from Mean, %	Av. Error, %
Synthetic mixture	Acetylsalicylic acid	53.52	53.31	55.06	54.33	54.75	54.36	±0.6	+1.6
	Acetophenetidin	38.34	38.36	37.12	37.74	37.96	37.79	−1.0	−1.4
	Caffeine	7.65	8.31	7.81	7.92	7.28	7.83	±3.6	+2.3
			Tablet Assays						
	Component	Labeled Composition, mg.	Run 1, mg.	Run 2, mg.	Run 3, mg.	Run 4, mg.	Run 5, mg.	Run 6, mg.	Mean, mg.
Tablet A	Acetylsalicylic acid	226.8	223.53	216.14	221.56	235.10	221.17	222.10	223.14
	Acetophenetidin	162.0	168.35	172.61	167.92	162.66	166.29	166.92	167.45
	Caffeine	32.4	32.4	32.4	31.72	31.34	33.70	32.10	32.28
Tablet B	Acetylsalicylic acid	226.8	224.64	217.04	226.36	227.70	225.23	...	224.19
	Acetophenetidin	162.0	161.78	170.21	161.48	160.00	162.16	...	163.11
	Caffeine	32.4	34.75	33.87	33.28	33.45	33.78	...	33.85
Tablet C	Acetylsalicylic	226.8	217.36	218.29	224.14	...	...	...	219.92
	Acetophenetidin	162.0	169.30	169.61	165.35	...	...	...	168.09
	Caffeine	32.4	33.98	32.77	31.17	...	...	...	32.64

SUMMARY AND DISCUSSION

GLC has been investigated with respect to its applicability to dosage forms containing APC mixture. It was felt that (*vis-a-vis* the N.F. column chromatographic technique) a method might be developed that would permit a greater number of replicate samples to be assayed, obviate the need for daily preparation of uniform columns, and release spectrophotometric facilities for other use.

This paper reports preliminary findings *via* a single-run type of assay. The results indicate that while the reliability of a single assay is less than in the official method, the means of the runs performed yielded results close to either labeled claim or composition by synthesis.

Efforts are being made to increase the precision of the technique and results will be reported in a future paper.

Communications

Possible Error in the Use of Polynomial Approximations in Urinary Excretion Rate Studies

Sir:

The utilization of urinary excretion data for the estimation of absorption rates has been employed in several reported studies (1–3). These papers indicate the method has certain advantages over one which bases its calculations on the concentration of the drug in blood plasma. Even though direct determination of plasma concentration of drug is recognized as a more accurate procedure, urinary excretion data are frequently employed since samples may be obtained at greater frequencies with a minimum of inconvenience to the subject, and drug concentration is such as to preclude assay difficulties.

Theoretical considerations of urinary excretion kinetics as related to absorption rate are reflected in the equation

$$dAe/dt = KfA_b$$

where dAe/dt is the rate of drug excretion; $K = 0.693/t_{1/2}$ where $t_{1/2}$ is the half-life of the drug in the body; f is the fraction of drug which is excreted in the urine unchanged; and A_b is the amount of drug in the body fluids. This equation is valid when the drug in the plasma is in equilibrium with other tissues and fluids of distribution. On the basis of this direct proportionality between excretion rate and the amount of drug in the body fluids, it is apparent that measurements of excretion rates plotted against time are far more indicative of rate of drug absorption than are plots of cumulative amounts of drug in the urine *vs.* time.

Excretion rates are defined as the instantaneous rate of change, at any given time, of cumulative

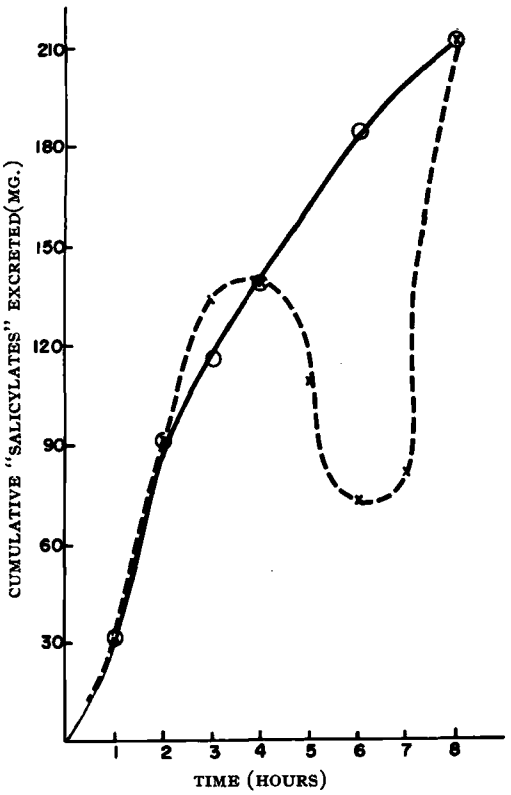

Fig. 1.—Comparison of actual and polynomial approximation curves. O, cumulative "salicylates" in urine in human subjects; X, polynomial approximations derived from 1, 2, 4, and 8 hour cumulative salicylate data.

amount of drug in the urine. Two basic methods may be used for their evaluation: graphical determination, or mathematical approximation of the Cumulative Amount *vs.* Time Curve with subsequent differentiation of the formula obtained.

The former method is tedious and requires a multiplicity of data for accurate determinations. The latter method, with the aid of a calculator, is to be favored both for rapidity and accuracy.

It has recently been proposed (2, 4, 5) that polynomial equations of fourth-order magnitude may be utilized to approximate the Cumulative Drug *vs.* Time Curve. The subsequent differentiation of the derived equations would directly yield the excretion rate at any time where the polynomial gives a good fit to the observed data.

The current literature in this area contains no reference to validation of reported data by a comparison of the instantaneous rates determined by polynomial approximation with either another approximation, or with graphical estimates. In addition, no graphical comparisons have been reported between experimental data and the polynomial approximation of these data.

Studies on excretion rates of salicylate currently being conducted in our laboratories indicate errors of rather large magnitude may be introduced in the mathematical treatment of data when using polynomial equations. The comparative plots in Fig. 1 indicate a possible degree of error which may be encountered in such approximations. The polynomial curve was derived from the actual cumulative salicylate levels of 30.5 mg. at the first hour, 90.3 mg. at the second, 138.9 mg. at the fourth, and 212.6 mg. at the eighth hour after ingestion. These data, obtained from one human subject, are typical of results obtained with other subjects in the study.

These results yielded the equation

$$x = -5.556t + 48.801t^2 - 13.766t^3 + 1.021t^4$$

where t is the time in hours and x equals the approximated cumulative milligrams of salicylate in urine.

In an effort to determine whether the range of the curve exercised any control on the accuracy of the approximation, a shorter plot covering the first 4 hours was calculated. The cumulative milligrams of salicylate at the third hour was 116.4 and this point, together with those for the first, second, and fourth hours, were utilized to derive

$$x = -28.43t + 88.83t^2 - 33.78t^3 + 3.88t^4$$

The fourth hour comparative curves in Fig. 2

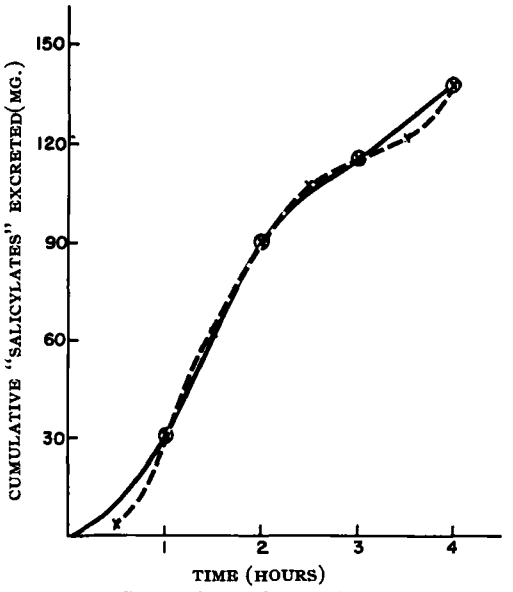

Fig. 2.—Comparison of actual and polynomial approximation curves. O, cumulative "salicylates" in urine in human subjects; X, polynomial approximations derived from 1, 2, 3, and 4 hour cumulative salicylate data.

indicate the degree of error is decreased, but it is evident that the deviations are such as to preclude the use of polynomials in this case.

The actual extent of error in the determination of excretion rate is more apparent when a comparison is made between rates obtained by graphical methods with those of the 4-hour polynomial equation. The graphical determination at the first hour is 63 mg.-hr.$^{-1}$, 43 at the second hour, and 22 at the third. The differentiated polynomial yielded values of 63, 46, and 11 mg.-hr.$^{-1}$, respectively. Good approximation is evident only up to the 2-hour level.

Polynomials are valid only when the curve being approximated tends to be parabolic either in its entirety or in the segments which compose it. The approximating equation to be used for a particular curve, or sets of curves, will depend on the nature of the curve and must be selected with consideration of its shape.

Based on these observations, we suggest that polynomial approximations be utilized with caution in excretion rate determinations.

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Book Notices

A Survey of Cardiac Glycosides and Genins. By J. HAMPTON HOCH. University of South Carolina Press, Columbia 1, S. C., 1961. 94 pp. 20.5 × 26 cm.

An exceptional reference source in a special field, this book includes tabulated information on plant sources of cardiac glycosides and genins, hydrolytic products of natural glycosides, and animal assay doses of natural and semisynthetic compounds. Structural features of compounds are grouped, and a discussion on structure-activity relationships is included.

General Pharmacology. By JEAN SICÉ. W. B. Saunders Co., West Washington Square, Philadelphia 5, Pa., 1962. ix + 593 pp. 16 × 25 cm.

This textbook on general pharmacology covers the pragmatic, biochemical and pharmacodynamic properties of the major classifications of drugs. General topic headings include: Physicochemical basis of pharmacodynamics, The ions, Cholinergic agents, Cardiac drugs, Smooth muscle relaxants, Conduction anesthetics, Histamine and antagonists, Adrenergic agents, The cerebral stimulants, The Cerebral depressants, Hormonal analogs and antagonists, Anticoagulants and inhibitors, Hematopoietic agents, Radioprotective agents, Antirheumatic analgesics, Antimicrobial agents, Anthelmintics, and Insecticides. Specific and general references of varying scope are provided at the end of each chapter. The book will probably prove most useful to the beginning pharmacology student.

Curare and Curare-like Agents. Edited by A. V. S. DE REUCK. Little, Brown and Co., 34 Beacon St., Boston 6, Mass., 1962. vii + 103 pp. 12 × 18.5 cm. Price $2.95.

This book reports the papers presented and discussions of the Ciba Foundation Study Group No. 12. The contents includes: The fate of curare during curarization, Influence of curare on uptake and release of neuromuscular blocking agent labeled with ^{131}I, Drug-receptor interactions at the neuromuscular junction, Structure-action relations throwing light on the receptor; and Experimental hazards and artefacts in the study of neuromuscular blocking drugs. The discussions following each presentation as well as a general group discussion which concluded the session are reported.

Pulmonary Structure and Function. Edited by A. V. A. DE REUCK and MAEVE O'CONNOR. Little, Brown and Co., 34 Beacon St., Boston 6, Mass., 1962. xv + 403 pp. 14 × 20 cm. Price $11.50.

This is another volume in the Ciba Foundation General Symposia series covering the various ways normal pulmonary ventilation is disturbed by disease and the effects in the alveoli. Paper topics include: Recent advances in pulmonary anatomy, Bronchial gas flow, Cellular structure and mucus activity in the bronchial tree and alveoli, Ventilation-perfusion relationship, Pulmonary gas exchange measurements using radioactive gases, Pulmonary capillary blood flow and gas exchange, Techniques used in the study of lung pathology: the anatomy of emphysema, and The degree of variation of blood perfusion and of ventilation within the emphysematous lung and some related considerations. Papers on other topics and discussions are included in the book. Author and subject indexes are appended.