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Pharmaceutical Sciences—1970: Literature Review of Pharmaceutics

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Keyphrases ☐ Pharmaceutical sciences—1970 literature review of pharmaceutics ☐ Technology, pharmaceutical—dosage forms, sterility, packaging equipment ☐ Physical pharmacy—dissolution, solubility, complexation ☐ Surface phenomena—pharmaceutical applications ☐ Crystallization, rheology—pharmaceutical applications ☐ Antibiotics—pharmaceutical aspects ☐ Biopharmaceutics—drug properties, absorption, pharmacokinetics

CONTENTS

This review of the literature represents a comprehensive cross section of the research and development efforts in various selected disciplines of the pharmaceutical sciences. It is the ninth annual survey in the series (1–8). To compile it, numerous periodicals and selected sections of *Chemical Abstracts* were abstracted.

The review was prepared to provide an opportunity for reviewing the research of the past year in specific areas of pharmaceutical sciences and to supply a convenient source of references to articles of preferred interest. The format of last year's review was retained because of its generally wide acceptance.

GENERAL PHARMACY

A comprehensive review of medicinal, chemical, and physical properties of the prostaglandins was presented. Possible pharmaceutical products of this group of potent hormones were also noted (9). The current status of drug compounds from marine sources was intensively reviewed (10). Marine organisms that showed different pharmacological effects and

Table I—Additional References on General Pharmacy

Reference	Topic
17	Method of organoleptic testing
18	Factors influencing preparation of stock tinctures
19	Review of cyclamates
20	Uses and importance of glycerol and glycerol substitutes
21	Function and composition of hormones, enzymes, and their interrelation with pharmaceuticals

potential as drugs were stressed. The potential of antimicrobial substances from the sea was also explored (11). Specifications in control of product uniformity were considered by several authors (12–14). Deficiencies in the control procedures set forth in various pharmacopeias were described, and suggestions aimed at improving the procedures were made. The neutralizing capacity of antacid drugs was evaluated by several authors (15, 16).

Other papers of interest in general pharmacy are listed in Table I.

Preservatives—A potentiating effect of phenylmercuric acetate on hexachlorophene or dichlorophene was observed in both *in vitro* and *in vivo* experiments (22). The results of a number of scientific investigations on boric acid were reported as ample evidence for eliminating this substance as a pharmaceutical agent. The risk of boric acid poisoning far outweighed its weak bactericidal power (23). Corticosteroids, such as cortisol and methylprednisolone hemisuccinate, were shown to reduce significantly the antibacterial activity of dodecyldi(β-hydroxyethyl)benzylammonium chloride and dodecyltriphenylphosphonium bromide against *Staphylococcus aureus* and, to a lesser degree, *Bacillus pyocyaneus* (24). Polyethylene glycol stearates decreased the antibacterial effects of phenols against *S. aureus*, but polyethylene glycols had little or no influence on the antibacterial activity (25, 26).

Equilibrium dialysis studies indicated a rather generalized binding of antimicrobial agents by cetomacrogol 1000 and polysorbate 80. The degree of interaction appeared to be dependent upon the type of functional group in the interacting molecule (27). The preservative activity of parabens in the presence of a polysorbate 80–water system was found to be related to the concentration of the free or unbound paraben (28). Prediction was made of the required preservative concentration for an emulsified system from a knowledge of oil–water partition coefficients, and preservative–macromolecule binding data were illustrated. In emulsions, the addition of a preservative to each phase was suggested as the best way to prevent excessive concentration of the agent in one of the phases (29). Thus, an ionizable preservative, such as a tertiary amine, is suitable for the aqueous phase; a nonionizable substance, such as benzyl alcohol, is most adequate in the oil phase. In an aqueous parenteral vehicle containing polysorbate 80 and benzyl alcohol, turbidity was found to be a function of concentration and temperature (30). The presence of electrolyte depressed the cloud point and brought the turbidity close to room temperature.

A study of the influence of dimethyl sulfoxide on the hemolytic activity of antimicrobial preservatives concluded that dimethyl sulfoxide affects the rate of preservative-induced hemolysis, probably due to a cellular mechanism rather than to an extracellular preservative–dimethyl sulfoxide chemical interaction (31). The release effect of benzalkonium chloride and hexachlorophene from various oil vehicles for the treatment of children's skin was studied (32). The best diffusion was obtained with a silicone solution and a 9:1 mixture of liquid paraffin–butyl stearate.

Different thresholds of cetyltrimethylammonium bromide uptake by *Escherichia coli* exist below which no effect on cell growth or viability could be detected (33). There was a distinct separation of the two effects. The antibacterial activity of various preservatives in several ointment bases was investigated (34). In general, the preservatives were more effective in paraffin and ophthalmic ointments. The most active preservatives were dodecyldimethylbenzylammonium chloride at 1:10,000 dilution and 0.2% sorbic acid.

Other papers of interest on preservatives are listed in Table II.

Table II—Additional References on Preservatives

Reference	Topic
35	Review of factors influencing stability and activity of antimicrobial preservatives for single-phase parenteral preparations
36	Review of antimicrobial agents in pharmaceutical products
37	Discussion of available preservatives and current practices in preservation of ophthalmic, nasal, and otic products
38	Stability and efficacy of combinations of preservatives for eye drops
39	Adsorption of preservatives on particulate solids in aqueous suspensions
40	Adsorption of various preservatives on membrane filters
41	Antimicrobial activity of some β-nitrostyrenes
42	Thermodynamic activities of monocomponent and multicomponent solutions of quaternary ammonium antibacterial agents

Flavor, Aroma, and Color—An encyclopedic evaluation of the literature in the perfumery materials field was continued by Bedoukian (43) in his 26th annual review. In a series of reports on odor measurement and its factors, additional evidence was presented on olfactory equilibrium and other aspects of odor theory (44). A primary odor, represented by isovaleric acid and its homologs and isomers, was correlated with molecular shape by a scanning computer method (45). The production of this primary odor required the carboxylic acid functional group in conjunction with a limited range of molecular shapes and sizes. A scientific evaluation of flavors was made (46), and a survey was conducted on the usefulness of fatty aliphatic compounds as components in the creation of natural flavors and fragrances (47). The effect of antioxidants on the oxidation of nine essential oils was investigated (48). α-Tocopherol citric acid was observed to be a remarkable antioxidant in lemon oil.

Stability—A set of computer programs and the system that automatically schedules all the assays necessary for a drug stability program was described (49). The effect of antioxidants on the hydrolytic and oxidative degradation of sulfacetamide in aqueous solutions

was investigated (50). Sodium metabisulfite accelerated the hydrolytic degradation of sulfacetamide to sulfanilamide, whereas sodium edetate had no effect on the rate. The sulfanilamide present in a heat-degraded solution had a major role in color formation under photolytic conditions. γ-Radiation-induced oxidation of aqueous pharmaceuticals can often be eliminated by customary antioxidants (51). Potassium bisulfite proved to be most effective in cyanocobalamin solutions and afforded suitable protective action in solutions of atropine sulfate, ephedrine HCl, hydrocodeine bitartrate, and ascorbic acid. Oxidative degradation of other drugs was presented in a series of papers (52–54).

In a study of the stability of drug solutions subjected to hydrolysis by ultrasonic irradiation, it was found that aromatic esters suffered structural changes. Aliphatic esters were resistant to such changes (55, 56). An investigation of the thermal dissociation of tolbutamide in a series of aliphatic alcohols and in polyethylene glycol 400 showed that the compound dissociates in only one fashion to give butylamine and *p*-toluenesulfonyl isocyanate (57). The thermal and radiation stability of labeled chlormerodrin and labeled diiodofluorescein also received attention (58, 59). The influence of sterilization, pH, and storage on the stability of aqueous injectable solutions of atropine (60), chlorhexidine (61), levarterenol (62), and scopolamine hydrobromide (63) was noted. The best stabilizer found for a sterile, concentrated, Ringer solution with glucose was calcium disodium ethylenediaminetetraacetate in the presence of HCl (64). The proposed acetylation of acetaminophen by acetylsalicylic acid was not evident in experimental pharmaceutical dosage forms (65).

A study of the incompatibility of 32 different amines with lactose alone or with magnesium stearate or stearic acid failed to show a dependence of the discoloration on the kind of amine (primary, secondary, tertiary, or quaternary) or on the change of pH (66). The stability of isoniazid and its derivatives was affected by blending with antacid preparations (67). Compounding aminophylline with acetylsalicylate, sulpyrin, hydralazine (Apresoline), sulfamethoxazole (Sinomin), ascorbic acid, and Panvitan should be avoided because of degradation (68). Similar compounding studies showed that when preparations of digestive enzymes are compounded with other drugs, the materials should be kept dry to preserve their activities (69).

An interesting article by Nogami *et al.* (70) was concerned with the hydrolysis stabilization of acylcholinesters by sodium lauryl sulfate at pH 7.7. Solubilization of acetylcholine–lauryl sulfate ion pairs in the micellar phase was proposed as the stabilization mechanism. A comprehensive review on the decomposition of aspirin included a complete survey of the hydrolysis studies to which this important compound has been subjected (71). The conditions for the highest stability of *Purpurea* glycosides A and B in tablet formulations were: neutral pH of the granulation mixture with a short drying time, low compression pressure of the tablets, and low temperature for storage of the tablets (72).

Table III—Additional References on Stability

Reference	Topic
73	Review of oxidative degradation of various drugs
74	Stability of a benzoyl peroxide acne cream product
75	Stability of three model suppository combinations, including appropriate excipients and additives
76	Stability study of chloramphenicol in British Pharmaceutical Codex topical formulations
77	Stability of dexamethasone ointments prepared with aquasorb or cetanol ointment
78	Thermal stability of antazoline chloride and naphazoline chloride in aqueous solution
79	Conversion of cotarnine in aqueous solutions
80	Review of stabilization of phenothiazine solutions
81	Effect of temperature and organic solvents on stability of ketazon
82	Influence of moisture, light, and air on stability of ketazon
83	Stability of benzothiadiazine derivatives in alkaline solution
84	Review of stability of morphine in opium
85	Preparation of more stable infusion solutions of sodium *p*-aminosalicylate
86	Stabilized aqueous suspensions of acetylsalicylic acid
87	Discussion of a comprehensive stability testing program for parenteral products
88	Stabilities of hexobarbital sodium and phenobarbital sodium in frozen aqueous solutions
89	Principles and techniques of accelerated storage testing and methods used for accelerating chemical and physical degradation processes
90	Stability of a prolonged-action aqueous suspension
91	Thermal stability of oxytocin in aqueous solutions and in the presence of glucose, sucrose, glycine, and sodium chloride
92	Compatibility of ointment bases with a 5% aqueous solution of methylcellulose
93	Stability of immune serum globulin during storage
94	Effect of excipients and storage conditions on stability of acetylsalicylic acid-based gels
95	Effect of chemical compounds, light, temperature, and humidity on pure gelatin capsules
96	Stability of glyceryl trinitrate tablets
97	Aminophenazone tablet decomposition during accelerated aging

Other interesting papers related to the topic of stability are listed in Table III.

Stability Kinetics—Evidence was presented to show how the salt effect in kinetic investigations may be extended to higher concentration ranges than expected by theory (not more than 0.01 *M*). Deviations from the Debye-Hückel expressions by the charged reactants and by the transition complex may be of the same magnitude and sign; this, it was claimed, may be the cause for the concentration range extension (98). The rationale of predicting the stability of pharmaceutical preparations using chemical kinetics was presented, using hydrocortisone sodium succinate as an example (99). Similarly, another author showed that in developing formulations of new compounds, kinetic studies were of great advantage (100).

A system of using computer tables and printouts for interpreting and predicting drug stability data was presented by Lintner *et al.* (101). This approach was developed to select the best prototype preparation, by giving an inkling of its chemical stability at an early date, and to estimate the shelflife of the finished dosage form. A flexible nonisothermal stability method was described, which permits the use of data from a single experiment to calculate activation energy, reaction rates, and stability predictions at any desired

temperature (102). The validity of the theory and the advantages of the method were demonstrated by a study of the inversion of sucrose and the hydrolysis of ethyl acetate. Bentley (103) presented a statistical technique for predicting thermal stability based on weighted least-squares analysis, which can easily be adapted for computer analysis.

Pawelczyk and his coworkers (104–111) investigated the kinetics of drug decomposition for a number of compounds. Investigation of the effect of 10 metal ions on the autooxidation of aqueous solutions of papaverine HCl showed that the most prominent effect was exerted by copper (Cu^{+2}) (104). The degradation was an apparent second-order reaction, and the catalytic activity was independent of the pH over the range studied (pH 2.3–4.15). The autooxidation of eupaverin in aqueous solutions was a second-order reaction and was relatively slow in the absence of traces of heavy metals. A comparison of their activation energies and 10% decomposition times indicated that eupaverin was approximately 2.5 times less stable than papaverine HCl (105).

The decomposition of antazoline in aqueous solution was first order and was independent of ionic strength and the kind and concentration of buffer (106). This drug was stable in acid solutions; the time of 10% decomposition of a pH 5.9 solution at 20° was 8.9 years. The decomposition of isonicotinic acid hydrazide in aqueous buffers between pH 3 and 7 was first order under anaerobic conditions (107). The greatest stability from solvolysis was observed at pH 6. Hydrolytic decomposition of phenylbutazone sodium was predominant in injectable preparations, and oxidative decomposition was predominant in suppositories (108). Phenylbutazone decomposition in various suppository bases followed a fractional-order reaction (109). In general, stability decreased with an increasing hydroxyl number of the suppository base. However, in aqueous buffer under nitrogen, the hydrolysis rate for sodium phenylbutazone was first order (110) and was independent of the kind and concentration of buffer, ionic strength, and hydroxyl-ion activity. The kinetics of quinidine sulfate decomposition in aqueous solutions were studied under the influence of light and heat (111). The decomposition at 353–363°K. was a first-order reaction; the light-induced decomposition was a zero-order reaction.

The stability of aminophenazone in aqueous solutions was examined in a series of papers. The decomposition of aminophenazone followed first-order kinetics, with maximum decomposition occurring at pH 6 (112). The decomposition activation energy was 9.280 kcal./mole. The characteristics of the degradation products in aqueous solutions were also examined (113). The stability of an aqueous formulation of aminophenazone stabilized with various oxidants was determined (114). The rate constants for the given stabilizers compared with a control indicated some improvement. A classical kinetic study employing the Arrhenius equation was used to predict the stability of taurinophenetidine at 25° in various pH solutions (115). The degradation kinetics were pseudo-first-order. In a similar study, 4-(aminoethanesulfonylamino)antipyrine in solution was examined at different pH's (116). By means of these kinetic studies, it was observed that the chemical in aqueous solution was practically stable at room temperature.

Kinetic examination of the stability of 2-diethylaminoethyl-3-methyl-2-phenylvalerate methobromide and its tertiary amine, 2-diethylaminoethyl-3-methyl-2-phenylvalerate hydrochloride, in aqueous solution showed that both undergo hydrolysis and follow a pseudo-first-order reaction (117). Stability of the quaternary ammonium salt and tertiary amine did not differ greatly, based on a comparison of their acid rate constants. However, comparison of their alkaline rate constants indicated that the tertiary amine was considerably less stable than the methobromide. Additional studies by Nogami *et al.* (118), with respect to the stability of some aminoethyl esters of phenylacetic acid, revealed that there was a linear relationship between λ (polar substituent constant) of R in $C_6H_5CHRCOOCH_2CH_2N(C_2H_5)$ and k_H or k_{OH}, and that the Taft formula could be applied to it. In addition, there was a linear relationship between the pKa and hydrolysis rate of the substituted esters. Additional studies of phenylacetic acid derivatives having a quaternary carbon at the 2-position indicated that the presence of steric hindrance in the position close to the ester linkage was very effective in stabilizing aminoalkyl esters (119). Rate constants were determined by Washkuhn *et al.* (120) for the alkaline hydrolysis of 36 *p*-substituted alkyl benzoates, and it was shown that these esters can be characterized on the basis of their rates of alkaline hydrolysis. Application of linear free energy relationships allowed a calculation of alkaline hydrolysis rate constants for alkyl or aromatic *p*-substituted benzoate esters not included in this study.

Murthy and Rippie (121) studied the effect of solvent anisotropicity on ester hydrolysis in lyotropic liquid crystalline phases. The reactions, as they occurred within the smectic phase, were characterized by relatively low apparent activation energies and by large negative entropies of activation. The hydrolysis of four carbonate and five carboxylic acid ester prodrugs of acetaminophen was determined in aqueous buffers at various pH's (122). The results suggested that it should be possible to formulate pharmaceutically stable suspensions of this type of drug. Mixtures of two amorphous alumina gels of different acid reactivity changed physically and chemically upon aging until a constant state was reached. The rate of conversion was found to be first order, temperature dependent, and directly dependent on the initial concentration of the less reactive gel (123).

The kinetics and mechanism of degradation of an allylic phosphate were studied as a function of pH and temperature by Oesterling and Gustafson (124). The activation energy for phosphate ester hydrolysis was 21.5 ± 0.9 kcal./mole. In the case of the solvolysis of methylprednisolone-21-phosphate, Flynn and Lamb (125) observed that there was an acceleration of reaction velocities and marked deviation from the expected pH dependency in more concentrated solutions (>0.02 *M*). This behavior was attributed to

association colloid formation. The rates of deamination of cytarabine, cytidine, and cytosine were compared in the presence and absence of catalytic buffers (126). Cytarabine exhibited only general acid catalysis, while cytidine and cytosine exhibited both general acid and general base catalyses. The hydrolysis of pilocarpine in aqueous solution was catalyzed by both hydrogen ion and hydroxide ion (127). Based on appropriate kinetic calculations, an optimum condition for the preparation of pilocarpine ophthalmic solution was suggested.

Other stability kinetic papers are listed in Table IV.

Antibiotic Stability—The kinetics and mechanism of degradation of clindamycin in buffered aqueous solutions were investigated by Oesterling (140). The antibiotic showed maximum stability at pH 3–5; however, high temperature studies indicated that not more than 10% degradation occurs in the pH range of 1–6.5 after 2 years at 25°. In a similar manner, the aqueous stabilities of lincomycin-2-phosphate and clindamycin-2-phosphate were studied at a variety of temperatures and pH values (141). Apparent first-order rate constants of phosphate ester hydrolysis, as well as activation energies (32.1 kcal./mole for lincomycin-2-phosphate and 32.9 kcal./mole for clindamycin-2-phosphate), agreed favorably. Stability studies of an antifungal antibiotic in selected ointment bases indicated glycerin monostearate was the most suitable (142). Ampicillin and carbenicillin stability in commonly used infusion solutions were investigated (143). Ampicillin showed wide variations of stability in the different vehicles, with least stability in solutions containing lactate ion; carbenicillin gave less than 10% decomposition over 24 hr. in all vehicles except 0.9% sodium chloride, in which 30% activity was lost. The degradation of a new synthetic broad-spectrum penicillin, 6-(1-aminocyclohexanecarboxamido)penicillanic acid, in aqueous solution at 37° was elucidated by the pseudo-first-order kinetics. This antibiotic was acid stable and was considered suitable for oral administration (144).

Systematic studies were carried out to prepare stable solutions of tetracycline HCl for intramuscular injection (145). A formulation containing 50–60% propylene glycol and filled under anaerobic conditions gave the most improved stability. The effects of pH, aliphatic oxyacids, vehicle type, sodium pyrosulfite, sodium bisulfite, and inert gases on the stability of tetracycline and its complexes with urea, calcium chloride, and sodium hexametaphosphate were studied (146). All showed maximum stability in weak acid media (pH 4–5), and their stability was influenced variably by lactic, citric, tartaric, and ascorbic acids: lactate gave maximum stability and ascorbic ion gave minimum stability. During microbiological determinations of chlortetracycline in riboflavin-containing solutions, the photolytic decomposition of riboflavin deactivated the antibiotic (147). Ascorbic acid or sodium thiosulfate was added to prevent this deactivation.

A study of streptomycin stability in aqueous solutions as a function of pH and temperature showed maximum stability at pH 4.0–5.0 (148). The effect of some B vitamins on the stability of dihydrostreptomycin sulfate in syrupy solutions was studied by accelerated stability methods (149). Both riboflavin and nicotinamide had a destructive effect on the antibiotic; thiamine hydrochloride had a slight destructive effect, while pyridoxine hydrochloride and pantothenate had a stabilizing effect. Dry oleandomycin phosphate, stored in evacuated containers, maintained activity within permissible limits for 1 year (150). Thermal sterilization of formulations of this antibiotic was not advised.

Additional references on antibiotic stability are presented in Table V.

Vitamin Stability—The sterically hindered vitamin A α,α-dimethyl palmitate was considered more resistant to autooxidation and more stable in the presence of the acidic emulsifier, diacetyl tartaric acid monoglycerides and diglycerides, than commercial vitamin A palmitate (159). Corn oil appeared to retard the loss of vitamin A ester potency due to acid-catalyzed degradation and isomerization. As part of a study of the stability of vitamin A, the results of a study on the stability of retrovitamin A acetate, an intermediate product of vitamin A acetate in aqueous ethanolic solution, was described (160). In a series of papers, the stability of vitamin A palmitate in selected ointments was discussed (161, 162). Generally, the vitamin was more stable in white than in yellow petrolatum; its stability in lanolin, freed of peroxides, depended on the acidity of the ointment base. Fairly stable ointments were prepared in eucerine and petroleum jelly. The stability of prepara-

Table IV—Additional References on Stability Kinetics

Reference	Topic
128	Stability of khellin
129	Effect of some hydrotropic salts on base-catalyzed degradation of khellin
130	Scheme for evaluating all new drugs by means of preformulation kinetic studies
131	Application of variable temperature kinetics with absolute reaction rate theory
132	Kinetics of hydrolysis of dimethylaminoethyl *p*-chlorophenoxyacetate hydrochloride
133	Salt effects on rates of alkaline hydrolysis of acetylsalicylate and acetylmandelate ions
134	Kinetic parameters necessary for evaluating stability of heat-sterilized pharmaceutical solutions
135	Hydrolysis of diamorphine in aqueous solutions
136	Comparison of stability programs for injectable phenobarbital solutions
137	Stability of phenylephrine hydrochloride in intravenous solutions
138	Kinetic study of aqueous solutions of sodium sulfacetamide
139	Oxidation of aqueous sulfite solutions

Table V—Additional References on Antibiotic Stability

Reference	Topic
151	Aqueous stability of triacetyloleandomycin and propionylerythromycin laurylsulfate; preparation of dry granules for reconstitution
152	Stability to heat and subsequent storage of chloramphenicol eye drops
153	Stability of mycetin D-17 during storage
154	Stability of chlortetracycline
155	Kinetics of degradation of tetracycline and 5-oxytetracycline and their initial degradation products
156	Stability of benzylpenicillin in aqueous solutions
157	Review of sodium methicillin in parenteral solutions
158	Review of factors influencing stability of penicillins

Table VI—Additional References on Vitamin Stability

Reference	Topic
178	Review of injectable solutions of water-soluble vitamins
179	Product acceptance factors in formulating a chewable multivitamin tablet
180	Stability of a vitamin A suntanning aerosol formulation
181	Improved stability of a vitamin B complex injectable by lyophilization
182	Review of kinetic studies on interactions and degradation reactions of ascorbic acid and thiamine
183	Physical stability of a tablet containing thiamine, pyridoxine, and cyanocobalamin
184	Degradation of thiamine in alkaline solution
185	Stability of vitamin C in various pharmaceutical preparations
186	Stability and mechanism of degradation of nicotinamidomethylaminopyrazolone
187	Stability of nikethamide solutions
188	Effect of copper ions on shelflife of vitamin C preparation

tions of vitamin A in a dry powdered form was studied (163). The combination of gelatin and dextrin plus 4.4% antioxidant was the most stable. In a series of papers, Bhattacharya (164–166) described the stability of various pharmaceutical vitamin A palmitate complexes in aqueous media. In general, the stability of vitamin A in an aqueous medium was much greater than in a dry state. The formation of anhydrovitamin A in these vitamin A complexes, which was dependent on the nature of the complex, was also elucidated.

The stability of thiamine hydrochloride in the presence of some antibiotics in capsules was determined by the use of accelerated stability methods (167). Tetracycline hydrochloride and chlortetracycline hydrochloride had some stabilizing action on the vitamin, but oxytetracycline hydrochloride and chloramphenicol had a destructive effect. A discussion of the mechanisms of stabilization of aqueous thiamine solutions by L-histidine indicated that the histidine complexes with metallic ions which cause the catalytic degradation (168). A kinetic study of pyridoxine hydrochloride in the presence of some antibiotics indicated that tetracycline and chlortetracycline hydrochlorides have a stabilizing effect on the vitamin, while oxytetracycline hydrochloride and chloramphenicol have a deleterious effect (169). The best container found for preserving aqueous solutions of cobamide (vitamin B_{12} coenzyme) against photolytic degradation was an amber borosilicate glass vial reheated to 650° (170). In other studies, cobamide in a lipoprotic vehicle remained more stable than when it was in an aqueous vehicle (171).

The effect of certain additives on the photochemistry of riboflavin was discussed in a paper by Shin *et al.* (172). It appeared from the compounds tested that an effective photochemical stabilizer should have a hydroxyl group, either attached to a benzene ring or in conjunction with the benzene ring. Light, pH, and heat affect the decomposition of folic acid injectable solutions (173, 174). Optimum stability was achieved at a pH value of 7.6. Vitamin K_1 in aqueous pharmaceutical preparations was relatively stable at pH 4.0–7.0 but unstable at higher pH (175). The degradation product in solution at the higher pH was isolated and identified. In addition, photolytic products of vitamin K_1 in the absence of oxygen were elucidated (176). An investigation of the influence of nonionic surfactants on the rate of degradation of menadione concluded that polysorbates (Tweens) stabilize the vitamin composition at neutral pH (177).

Other references pertaining to vitamin stability are listed in Table VI.

PHARMACEUTICAL TECHNOLOGY

The science and technology of microencapsulation, with applications in pharmaceutical and cosmetic fields, were reviewed by Luzzi (189) and Nack (190). In a series of review articles on aspects of pharmaceutical technology, a wide range of topics was discussed, including fluidization applications, pulverization with ball mills, polymeric film coating, and freeze-drying processes (191–195). Other articles outlined some effects of moisture, glidant addition, and mixing equipment on the flowability and mixing performance of bulk particle solids (196–198).

Parenterals—The effect of rubber closures on injection solutions was a topic of several interesting papers. The turbidity produced in aqueous solutions of viomycin, stored in glass vials and closed with rubber stoppers, was found by TLC and GLC to be caused by di-*tert*-butyl-*p*-cresol, tetramethylthiocarbamoyl disulfide, and mercaptobenzothiazole (199). In another similar study, stopper formulations containing zinc dithiocarbamates and thiurams caused much clouding; those containing 2-mercaptobenzothiazole, sulfenamides, or guanidines caused much less (200). Only very small amounts of turbidity were observed in solutions in contact with peroxide or phenol–formaldehyde resin-cured samples. Yanchick and Sperandio (201) studied the relative loss of benzyl alcohol-7-^{14}C when exposed to natural rubber, neoprene, and butyl rubber closures. In 1% solutions, the rate of loss depended on temperature and on the position in which the vials were stored; natural rubber gave the greatest loss and butyl rubber the least as temperature increased.

Precipitates found in admixtures of potassium chloride and 5% dextrose in water were identified as silica and alumina (202). Another study of particulate matter in intravenous solutions revealed that considerable variation existed in the same product from different manufacturers and in different solutions or different lots of the same solutions from the same manufacturer (203). The addition of devices or additives increased the number of particulates, but a final filter set was very effective. Particulate contamination in vials of sterile dry solids upon reconstitution was examined, using a membrane filtration technique and subsequent microscopic examination and counting of particles (204). Significant differences were found in particle counts, but not size distribution, in the products of different manufacturers. No significant fall in activity with time was observed in solutions of noradrenaline containing 5% dextrose, 5% dextrose in physiological saline, and acidified physiological saline (pH 3.6), but there was a significant loss of activity in physiological saline and 4.2% sodium bicarbonate solution (205). Parenteral admixtures of metaraminol

bitartrate and hydrocortisone sodium succinate with 5% dextrose in normal saline remained stable for at least 48 hr. (206). The buffer capacity and pH of a number of commercial infusion solutions were determined (207). For purposes of calculating pH after drug admixture, the buffer capacity of pure electrolyte solutions and dextrose or dextran fluids of pH 4.5 need not be considered.

A simple technique to control aseptically the required pH of solutions for the preparation of $^{113}In^{m}$-labeled ferric hydroxide particles was described (208). The advantage of the procedure was the elimination of autoclaving time, a critical factor when the nuclide has a short half-life. Residual biological activity of injectable solutions of cyano- and hydroxocobalamins after ^{60}Co γ-irradiation was higher than expected from photometric determinations (209). Solutions of high vitamin content were more resistant than low ones, hydroxocobalamin being more resistant than cyanocobalamin. A number of drugs sterilized by γ-irradiation showed little or no breakdown (210). However, in solutions of low concentration (mostly <0.5%), these compounds underwent extensive change.

Intravenous injection of 7,12-dimethylbenz[*a*]anthracene in dimethyl sulfoxide was judged to be at least as active as fatty emulsions now in use (211). Intravenously administered soybean emulsions of pentobarbital and thiopental prolonged the sleep time in mice compared with the corresponding aqueous solution (212). In another experiment, a similar effect was observed when helianthic and linseed oils, dimethyl sulfoxide, polysorbates 60 and 80 (Tweens 60 and 80), or propylene glycol was administered prior to hexobarbital treatment (213). The use of additives to enhance the stability of injectable solutions of a diethylamine salt of phenobarbital (214), reserpine (215), and esters of diphenylacetic acid derivatives (216) was reported. The effects of pH, solvent, light, metal ions, container, and oxygen content of solvent water on the stability of injectable L-ascorbic acid solutions were elucidated (217, 218). Maximum stability of the aqueous solution was found at a pH value of 6.5. Cysteine hydrochloride was used to stabilize dexamethasone-21-phosphate injectable solution sterilized by bacterial filtration (219). The best stabilizer of an injectable calcium gluconoascorbate was a mixture of 0.1% thiourea and 0.1% cysteine (220). The behavior of castor oil under conditions of thermal sterilization gave no indication that it required a more careful sterilization procedure than that used for peanut oil (221). Sterilization at 180° for 25 min. was recommended.

Other papers of interest in the category of parenterals are listed in Table VII.

Table VII—Additional References on Parenterals

Reference	Topic
222	Compilation of stability and compatibility problems of drugs in injections or intravenous infusions
223	Review of contamination of injectable solutions by perfusion and transfusion kits and other associated equipment
224	Critical discussion of particulate matter in solutions for injection and methods of determination
225	Description of apparatus for determining particulate matter originating in intravenous infusion sets
226	Effect of contact with metal equipment on stability of papaverine solutions for injection
227	Review of pharmaceutical uses of polyvinylpyrrolidone in parenterals
228	Incompatibility of drug mixtures for parenteral administration
229	Parenteral formulation procedures for investigational drugs in cancer chemotherapy
230	Compilation for preparation of solutions for injection using a weight–volume ratio
231	Incompatibility of commercial injections (298 combinations) as examined by TLC
232	Treatment of activated carbon used for purifying 40% glucose solution for injection
233	Demonstration of thermostability concept in preparation of sterilized aqueous solutions
234	Production of infusion fluids of low particle content

Sterility—The various sterilization processes employed in the pharmaceutical industry were reviewed and discussed (235). Methods of preparing sterile eye drops and ointments according to prescription were also described (236). The pattern of temperature rise in articles undergoing sterilization in an oven under normal working conditions was investigated by Peacock and Ridgway (237). Mathematical models, each expressed in terms of a set of differential equations, were fitted to the data obtained. Knowledge of the heating rate in a bottle of known volume permitted calculation of the rate in different size bottles containing the same liquid and undergoing the same heat treatment (238).

Various techniques for ethylene oxide sterilization were described and evaluated by Gunther (239). In another article, factors influencing the degassing of ethylene oxide-sterilized rubber and plastic articles and the toxicity of reaction products in these polymers were described (240). Ethylene oxide as a propellant and sterilizing agent was proposed as one method of assuring sterility in filled aerosol containers (241). An interesting paper by Chen (242) demonstrated the ability of 100% ethylene oxide to penetrate the silicone coating used on disposable hypodermic needles and syringe rubber plunger tips. Spores of *Bacillus subtilis* var. *niger*, introduced underneath the silicone coating, were killed by the ethylene oxide treatment. β-Propiolactone was put to a unique use in a method of sterilizing pig heart valves (243). An apparatus designed for sterilization with formaldehyde was described for use in pharmacy (244), and the parameters for effective formaldehyde sterilization were established.

Methods of radiation sterilization in the pharmaceutical industry were reviewed (245, 246). The effect of γ-radiation, as used in the radiosterilization of glass ampuls, on the resistance of glass containers was investigated. This radiation gave no lowering in classification of glasses in the hydrolytic resistant groups (247).

A membrane filtration procedure for testing the sterility of insulin zinc suspensions solubilized in ascorbic acid diluting fluid was a significant improvement over the direct method of sterility testing (248). The removal of abnormally large amounts of added pyrogens in 15 different standard infusion solutions by filtrations through an asbestos filter layer was investigated (249). The filtered solutions were pyrogen

Table VIII—Additional References on Sterility

Reference	Topic
250	Review of filtration methods for injection solutions
251	Review of use of gaseous sterilizing agents
252	Review of microbiological aspects of drug production
253	Discussion of factors to assure sterile water conditions
254	Significance of primary contamination testing in routine studies for rejection of ampul preparations

free, with the single exception of a high sugar content infusion.

Other papers relative to the subject of sterility are listed in Table VIII.

Tablets and Capsules—The factors affecting the compression of tablets were reviewed by Livingstone (255). Special emphasis was given to the operational steps necessary in direct compressions. In an excellent article by Fonner *et al.* (256), optimization techniques in drug product design and process analysis were presented. This method was applied to generate optimal formulations in typical tablet design problems and to locate optimizing variables in a typical encapsulation design problem.

The effect of several grinding variables on the flow characteristics of liquids and solids through a small continuous wet ball mill was investigated (257). It was found that none of the major grinding variables caused major changes in the form of the distribution (logarithmic normal) of residence time function. In one laboratory-scale fluid energy mill, a reduction in particle size to subsieve size was attained. The product particle-size distribution was very sensitive to feed rate (258). In exploratory experiments on kinetics of comminution, sodium chloride was milled in a ball mill at relative humidities of 0.5 and 4% for various periods (259). The particle size, as determined by sieve analysis, was reduced until the load no longer sufficed to break the particles. Thereafter, they agglomerated, particularly in drier air, and the agglomerate size increased with increased milling time. Some statistical methods for evaluating particle-size distribution were studied and compared (260).

The origins, nature, measurement, and effects of particle residual stresses were critically reviewed by Hirschhorn (261). The possible primary causes of residual stresses were listed as uniform and nonuniform plastic deformation, temperature and thermal strain differentials, and phase transformation in individual particles. The radiological techniques necessary to obtain quantitative geometric descriptions of particle packings (particles of any shape and a large range of sizes) were developed (262). A mathematical expression was given to the relationship between the number of equally sized spherical particles and the porosity of a unit cross section of a sedimentation bed resulting from the packing of powder (263).

Several interesting papers appeared on the mixing and blending of bulk pharmaceutical powders. The factors that contribute to the kinetic angle of repose of powders in the flights of rotary drums were shown to be particle size, drum speed, and the type of material (264). Measurements of the static angle of repose were statistically correlated with particle size. The mixing of components of similar size and density in a horizontal drum mixer were characterized by a parameter, the migration coefficient, which was used in developing a scale-up procedure (265). Segregation occurring when different particle sizes were present was investigated for a number of different drum mixers. An apparently randomized mixture was obtained when the drum was rotated at the speed at which the porosity of each component was maximum. An equation was derived for the variance of the composition of samples drawn from nonrandom binary mixtures (266). The index of mixing was equal to zero for no mixing and one for random mixing.

The present state of knowledge of continuous mixing was reviewed by Williams and Rahman (267). After considering available experimental techniques, a simple method suitable for solid mixers was described. It was shown that the performance of an inclined rotating drum mixer, investigated by the δ-input response technique, could be assessed for establishing the best operating conditions of a given system. In studies on the mixing of pharmaceutical powders, cohesive powders charged to the bottom of a V-type mixer behaved like "diffusion" from the charging position of the active ingredient (268). In an experiment to elucidate the mechanism of lubricant action in the operation of mixing and lubricating pharmaceutical powders with calcium stearate in a V-type mixer, a relationship was observed between the changing rate of apparent density of the powder and the cumulative revolution number of the mixer (269).

A good correlation was shown to exist between the flow properties of clomacran phosphate powder blend and capsule fill-weight variation when an automatic capsule-filling machine was used (270). Most of the weight variation of the finished capsules, also affected by lot-to-lot variability and concentration of the drug, was overcome by a granulation procedure. The apparent specific volume and the breaking strength of mixed systems found in granulating processes were investigated in relation to the filling properties of the systems (271). The changes in extrusion weight and other properties of the systems with the lapse of time in the process of granulation were discussed in relation to changes in particle compactness and breaking strength. The effect of properties of binder solutions was also investigated in the same mixed systems (272): the higher the viscosity of binder solution, the greater the tensile strength. In addition, it was found that the extrusion weight of granules through an extrusion-type granulator was inversely proportional to the breaking strength of the mixed system.

An investigation of the effect of particle shape on the variation of the fill in a tableting die found that the mean contained weight was greater for regular than for irregular particles (273). A maximum die fill occurred when the ratio of die diameter to particle diameter was about 20 for all particle shapes. The influence of glidants on the technical properties of tablet granulation was studied by comparing the weight variations of tablets with flow properties of the granulations, as measured by the angle of repose, the flow rate, and

the internal angle of friction (274). No correlation was observed between flow properties and weight variations of the tablets. In evaluating a glidant and in selecting its concentration in a tablet formulation, the homogeneity of the powder mixture and the possibility of segregation during preparation were considered (275).

Evaluation of a tablet-lubricating agent by electronic pressure measurements from an instrumented press was demonstrated for magnesium stearate (276). For every lubricant, a concentration could be established above which the friction conditions in the machine were not changed even with high compression numbers. Examination of a mixture of sodium bicarbonate and magnesium stearate, using an optical and a scanning electron microscope, showed that magnesium stearate formed a replicalike film over the surface of the bicarbonate particles (277). Flow regulation of powders of various particle size, form, and surface structure was studied with a preparation of aluminum hydrosilicate (278). This glidant exerted either a positive or negative flow regulation; thus, the optimum concentration must be determined for each powdered substance individually.

The effect of surface-active agents as lubricants for tablets on the release of active substances from compressed tablets was studied by comparing dissolution rates of some steroid formulations (279, 280). The concentration of the surface-active agents was not high enough to lower the surface tension of the solution significantly or to increase the solubility of the steroid, but their use as lubricants increased the release of the active ingredient. Similar effects were observed on sulfanilamide pellets and tablets (281). The differences in the minimum amount of polysorbate 80 (Tween 80) and poly(oxystearate)-40 required for the complete hydrophilization of powders for tablet manufacture were interpreted in terms of the various hydrophilic–lipophilic balance (HLB) values of the surface-active agents, different hydrophobicities of powders, and the different grain sizes of powder particles (282).

The influence of tableting pressure on the surface texture of tablets consisting of corn starch, lactose crystals, and cyproterone acetate microcrystals was examined by the scanning electron microscopic technique (283). Deformations of the starch grains in formation of solid bridges through the lactate and cyproterone crystals were observed. Tablets of magnesium carbonate placed in water disintegrated rapidly into their components, presumably due to breakdown of interparticulate bonds (284). Particles of known size were compressed and allowed to disintegrate to give evidence of fragmentation or interparticulate bonding. Moisture in tablets (2.5–6.6%) reduced the surface area. This was due to improved lubrication and, for more soluble substances, to recrystallization, which permitted the formation of interparticulate bonds (285). Similar effects of moisture on the compression of tablets were observed as a function of their apparent density (286).

The use of compression modulus to describe the effect of moisture on compression behavior was discussed by Rees (287). He presented data to show that, at higher pressures, it is insufficient to quote values of the pressing modulus unless the actual relations between pressure and relative volume are considered. Measurements of the temperature rise occurring on compression, recompression, and relaxation of tablets were investigated by means of thermocouples inserted in the compressed materials (288). With all tablets, a rise in temperature was observed on initial compression and a fall on relaxation. The temperature rise was further separated into two components: that due to compaction and a further rise due to elastic compression. In another investigation, the rise of temperature on the upper and lateral surfaces of tablets during compression was examined. The rise of temperature was linearly related to the logarithm of compression time or the logarithm of ejection force (289).

Tableting behavior of crystalline and spray-dried lactose as a function of particle size, shape, and storage of powders was examined under direct compression (290). The results indicated that particle size had little effect, but particle shape and storage influenced the strength of the tablets. Henderson and Bruno (291) found that lactose USP (beadlets) and dextrose (PAF 2011), two new agents for direct compression, were generally superior to the other materials they tested (spray-dried lactose USP and anhydrous lactose USP) for use as fillers for direct compression. Direct compression tablet formulations of phenobarbital, sodium phenobarbital, phenacetin, butyl scopolammonium bromide, and rutoside with tableting agents were described by several authors (292–294).

The rate of moisture uptake by loosely packed and tapped beds of six pharmaceutical materials was found to be independent of bulk density but dependent upon bed depth (295). The tensile strengths of the bulk solids changed when subjected to high relative humidities. The use of a microindentation apparatus to determine the hardness of tablets at various points on their diameter was described (296). This apparatus measured the total deformation at the loaded point on the tablet and also elastic recovery when the load was removed. The diametrical crushing strength of an ideal system of compressed particulate material and the relation between strength and mean compression pressure were found by Rees and Shotton (297) to depend on the time at which the strength was determined. Increases in strength of over 100% during the 1st hr. after compression were attributed to stress relief of the crystals and interparticulate bonds.

An investigation of the breaking strength of tablets containing lactose and microcrystalline cellulose showed that for tablets of 2–30-kg. nominal strength, an increase in the loading rate produced a significant increase in the breaking strength (298). These results, obtained using an Instron universal testing instrument and compared with those obtained using other instruments, indicated that discrepancies in the strength values may be partially attributed to differences in the rates of loading. The tensile strength of lactose tablets, as contrasted to crushing strength, was measured by applying the diametral compression test described by Fell and Newton (299). To obtain reproducible

results for the strength of tablets prepared at a given compression force, it was shown that the tablet must break in such a manner that the tensile strength is the major stress. Usually, there appears to be no way of quantitatively predicting the properties of tablets by considering the properties of the individual components. However, for a single material such as lactose which exists in three forms (α-anhydrous, β-anhydrous, and α-monohydrate), it was possible to predict the strength of tablets prepared from mixtures of the three forms from measurements of the strength of tablets prepared from the individual components (300).

The influence of a number of tableting parameters on the pore structure and disintegration characteristics of model tablet formulations was reported in a series of interesting papers. The addition of starch to the various tableting materials produced no significant effect on the pore structure of the dry tablet but caused disintegration of this structure when the tablet was penetrated by water (301). This effect was a function of the compressibility of the constituent materials and the pressure used to compress the tablet. In studying the effect of granule properties on the pore structure of tablets of sucrose and lactose, it was found that low pressure, high density, high strength, and large granule size promoted a more open but less uniform structure (302–304). Such conditions produced a bimodal pore-size distribution. Although conditions of wet granulation influenced the pore structure of lactose tablets prepared over a wide range of compression pressures, dry granulation only influenced pore structure when slugging pressures were high, the granules were coarse, and tableting pressures were low. The effectiveness of the disintegrating ability of starch was dependent on the solubility of the tableted drug; disintegration rates decreased with increasing water solubility of the drug (305). The beneficial influence of some crosslinked polyelectrolytes and crosslinked gum arabic in some difficult to disintegrate tablet formulations was reported by Hirata (306, 307), along with a discussion of the disintegration mechanism.

The adhesion of film coatings to surfaces of compressed tablets was examined by Wood and Harder (308) for the effect of the critical surface tension of a tablet surface and the surface tension of a coating solution and its components on the strength of the adhesive bond between the film coating and tablet surfaces. Tablets with higher critical surface-tension values had increased bond strength, but the hypothesis that decreasing the surface tension of the coating solution and balancing the surface tensions of the components to yield a positive system should result in increased bond strength was not clearly established by experimental evidence. Other experiments, conducted to characterize tablet surfaces by their critical surface-tension values, indicated that increased critical surface tension results in increased wetting by the coating solution and in an increased bonding force between the tablet surface and the polymer film coating after the solvent has evaporated (309).

A statistical analysis was made of the variation from tablet to tablet in the amount of drug in the coat of sugar-coated tablets. Although the standard deviation in a series of batches was linearly related to the square root of the number of coats, the plot failed to intersect at the origin and did not have the required slope (310). Apparently, other factors such as viscosity and surface activity of the syrup suspension, core shape, and pan build-up contribute to the variation. An improved self-programming automated tablet-coating system, based on the rate of moisture loss in the tablet mass, was designed and evaluated by Heyd and Kanig (311). A high degree of sensitivity of drying cycles to changes in environmental humidity in the coating pan was demonstrated. Methods and equipment found useful for recording temperature patterns resulting from the evaporation of volatile coating solutions applied to pellets in a rotating pan were discussed (312). These characteristic patterns were interpreted in regard to run-to-run replication, effect of application and drying rate, and coating-solution distribution. The manufacturing technique for titanium dioxide lakes, prepared from certified water-soluble dyes, and the pharmaceutical application in color-coating tablets were described and discussed in conjunction with automatic spray coating (313). Substances evaluated for enteric coating of tablets included polyglycerol stearate, poly(vinyl acid phthalate), gluten, gliadin, and glutenin (314–316). The feasibility of large-scale production of cellulose acetate phthalate enteric-coated capsules, based on the use of a fluidized-bed spray film coater, was discussed by Jones (317).

Further references of interest in the general area of tablets and capsules are listed in Table IX.

Suspensions—A model for rheological behavior of thixotropic systems was advanced for suspensions of rigid, solid particles in liquids (353), but it was not expected to be valid for materials of a polymeric nature or for suspensions of elastic, deformable particles in liquids. Some applications of rigidity and yield values in a study of gelatin and laponite gels were described (354). An important property of thixotropic hectorite gels was found to be the relatively rapid sol–gel transformation.

Depending on the concentration of a suspension, it will exhibit one of three sedimentation patterns pertaining to low, intermediate, and high concentrations of solids. The sedimentation kinetics of flocculated suspensions in the initial sedimentation region and the following intermediate region were investigated from both a theoretical and experimental standpoint by Carstensen and Su (355, 356). In the initial phase, it was shown that sedimentation data were consistent with theory. Empirically, these data can be evaluated by plotting the square root of height as a function of time; the slope of these lines appears to be proportional to the ratio of density difference to viscosity. Sedimentation of the intermediate phase presented as a theoretical equation was also supported by experimental data. A method of comparative analysis of sedimentation and Brownian motion was described for determining the maximum diameter of particles that will not sediment in an aqueous suspension (357). These calculations by a computer yielded valuable information as a guide to suspension formulation, but the presence of suspending agents nullified the method.

Table IX—Additional References on Tablets and Capsules

Reference	Topic
318	Discussion of a thixotropic agent (Aerosil) for the improvement of the flow characteristics of powders
319	Study of packing of irregular particles
320	Method for dielectric study of solid powders
321	Statistical analysis of uniformity of distribution of cyanocobalamin in tablet formulations
322	Fluidized-bed particle coating
323	Survey of research on powders done in the School of Pharmacy, University of London
324	Use of cordia myxia mucilage as a binder in tablet manufacture
325	Effect of various drying conditions on rates of drying of pharmaceutical preparations
326	Changes in physicochemical properties of a synthetic magnesium aluminum silicate due to hydrothermal treatment
327	Sampling approach to ensure tablet uniformity throughout a tableting run, and assessment of powder mixtures for cosmetics and pharmaceuticals
328	Preparation of fat-based pills using a Piluterm apparatus
329	Unique device for external lubrication of die in preparation of effervescent tablets containing nicotinic acid and sodium bicarbonate
330	Review of uses of mannitol in production of lozenges and chewable tablets
331	Preparation of sterile implants by compression
332	Formulation with microcrystalline cellulose of a morphine implantation pellet
333	Fusion for preparation of two-component tablets containing sodium salts of organic acids
334	Quality control method for determining tablet and capsule defects by visual inspection
335	Effects of cooling and granulation mixing time on amidopyrine tablets
336	Influence of humidity on granules in the compression of sodium salicylate and *p*-aminosalicylate
337	Effect of temperature and compression on tensile strength of compressed particles
338	Introduction of working bulk density as a concept in powder technology
339	Effect of methylene casein on the physical properties of tablets
340	Discussion of a disintegration apparatus for evaluation of drug availability
341	Comparative evaluation of seven dissolution apparatus for capsule dosage forms
342	Release of isoprenaline sulfate from certain sublingual tablet bases by disintegration time measurement
343	Effect of compression pressure on the disintegration of some sulfonamide tablets
344	Effect of powdered celluloses on the strength and disintegration rate of compressed tablets
345	Tabulation and discussion of tablet hardness and disintegration time measurements on 105 products
346	Principles, method, and apparatus for automatic coating of tablets
347	Review of enteric coatings
348	Influence of various additives on softening point of shellac films
349	All-glass laboratory apparatus for fluidized-bed coating of tablets or pills
350	Review of film coating of pharmaceuticals
351	Review of film moisture protective coatings for orally administered drugs
352	Manufacturing procedures of hollow gelatin capsules

Investigation of highly flocculated suspensions of clay in batch tests showed that the rate of formation of sediment of a given concentration decays exponentially with time from the start of a test (358), but established theory predicts that it should remain constant.

The influence of electrolyte, type and concentration of surfactant, and nature of vehicle upon the physical properties of sulfaguanidine suspensions was investigated (359). It was reported that acceptable suspensions of this drug were produced by controlled flocculation in the sulfaguanidine–polysorbate 80–aluminum chloride system. In a point of controversy, other authors presented data showing that flocculation cannot take place in this system (360). The effect of adding a wetting agent on the physical properties of sulfamerazine suspensions was described (361). When all the components were mixed totally and simultaneously, a more flocculated and more stable suspension was produced than when the wetting agent was added first, followed by the hydrophilic suspending agent. The effect of alcohols, surfactants, lipophilic materials, and temperature on the rate of sedimentation of aqueous talc and zinc oxide suspensions was reported (362–365).

In studies of the coagulation kinetics of mixed suspensions, Matthews and Rhodes (366) used a computer to predict the particle-size profile during the coagulation of a mixture of two normally distributed particulate suspensions; they tested the Müller equation for the coagulation of a mixture of large and small particles using the Coulter counter. A critical evaluation of the use of the Coulter counter model B in coagulation studies was made, and the implications of the effect of coarsening the suspension on the detection of small particles was discussed (367). Particle-size analyses of some pharmaceutical suspensions were made by the Andreasen pipet method, sedimentation balance, and the Coulter counter (368). As long as the particle-scattering coefficient was constant, controlled by the volume and surface area distribution functions, values from the pipet method yielded accurate results. The Derjaguin, Landau, Verwey, and Overbeek (DLVO) theory was used by Matthews and Rhodes (369) to interpret pharmaceutical suspension stability. Practical guidelines for formulation of suspensions by a coagulation technique were presented. The dispersibility of sulfisoxazole, sulfadimethoxine, and N_1-acetylsulfisoxazole in aqueous sucrose solutions containing polyoxyethylene nonyl phenyl ether or sodium lauryl sulfate were examined (370, 371). From these results, it was concluded that the dispersive sedimentation of sulfonamides began at the polyoxyethylene nonyl phenyl ether concen-

Table X—Additional References on Suspensions

Reference	Topic
372	ζ-Potential and its use in pharmaceutical technology
373	Review of pharmaceutical suspensions
374	Effect of carboxymethylcellulose on dehydration of kaolin suspensions in the filter press
375	Properties of Spanish agar
376	Interpretation of Beer's law curves for concentrated dye suspensions
377	Review of action of dispersing agents in pigmented aqueous dispersions
378	Stabilization of calamine lotion and milk of magnesia with carboxymethylcellulose or guar gum
379	Effect of nonionic surface-active agents sorbed onto organoclays on rheological properties of oleopseudogels
380	Criteria for estimating amounts of pectins of different viscosities in the manufacture of suspensions
381	Layering phenomena in colloidal suspensions
382	Settling characteristics of precipitated magnesium hydroxide suspensions

Table XI—Additional References on Emulsions

Reference	Topic
412	Influence of some emulsifiers on stability of cosmetic emulsions
413	Effect of emulsifiers on distribution of medicinals in emulsion systems
414	Emulsion-forming characteristics of complex emulsifier systems
415	Aging processes of model emulsions with complex emulsifier systems
416	Method involving ternary phase diagrams for developing stable emulsions
417	Demonstration of a ternary system in an aerosol emulsion preparation
418	Effects of solid additives on formation and separation of emulsions
419	Factors affecting stability of concentrated emulsions
420	Influence of nonionic surface-active agents on quality of o/w emulsions
421	Stability of emulsions using sodium dodecylbenzenesulfonate
422	Emulsion and aerosol formulation
423	Formulation of castor oil emulsion
424	Mechanism of emulsification in bidisperse systems

tration of about 1×10^{-3} mole/l., and the dispersibility was decreased by the addition of sucrose. In the case of sodium lauryl sulfate, the dispersive sedimentation began at 4×10^{-3} mole/l. and was not affected by the addition of sucrose.

Other articles relating to suspensions are listed in Table X.

Emulsions—Numerous review articles were published on the theory and practice of emulsions and microemulsions and the critical factors associated with emulsion systems (383–394). Characteristics of inclusions in the dispersed phase of liquid–liquid suspensions, a structure known as a double-multiple emulsion, were determined by an investigation of the hydrodynamic formation of these structures (395). A simplified model, based on the use of spray nozzle parameters, satisfactorily correlated percent included area and volume as a function of the Reynolds number and Weber number. An investigation of the phase equilibria on properties of an emulsion showed the presence of liquid crystalline phases and also explained the sudden changes in stability, viscosity, and even inversion that can take place with small changes in emulsifier concentration (396, 397). The influence of micelles in the system was also pointed out.

An interesting paper was presented by Garrett (398) on the prediction and evaluation of emulsion stability with ultracentrifugal stress. Nonstratified creams demonstrated an initially apparent first-order process of large particle drainage from the cream simultaneously with continuous drainage of the heavier surfactant. The final rate of oil separation was constant, reflecting the rate-determining coalescence at the cream–oil interface. Use of statistical experimental design studies on emulsification with various emulsifiers indicated that the stability was affected more by the volume ratio of the water phase than by the amount of emulsifier or method of mixing (399). The stability was also influenced by temperature. The stability of w/o emulsions as a function of temperature and of the hydrophilic chain length of the emulsifier was examined (400). Relatively stable w/o emulsions were obtained when the phase-inversion temperature of the emulsions was about 10–40° lower than the storage temperature. Differential thermal analysis procedures were described for determining the phase-inversion temperature of o/w emulsions stabilized by polyoxyethylene surfactants (401). With a given oil phase, the phase-inversion temperature increased linearly as the HLB of the surfactant increased. Different methods of determining emulsion stability and HLB of surfactants were the subjects of several papers (402–404). These procedures were based on measuring the intensity of reflected β-radiation, electronic counting with a Coulter counter, and measuring a characteristic change of viscosity at the stage of phase inversion.

The autooxidation of o/w emulsions was found to depend on the hydrogen-ion concentration (405). Oxygen uptake measurements and peroxide number determinations increased with rising pH up to a maximum at about pH 10 and then fell again at a still higher pH. Hydroxycarboxylic acid antioxidants suppressed the metal-catalyzed autooxidation of o/w emulsions (406). The chelating agents, citric and tartaric acids, were shown to inhibit oxidation of oil with low peroxide numbers, but this effect was not observed for ferrous ions in samples of high peroxide number.

Liquid paraffin emulsions, stabilized by cetrimide or sodium dodecyl sulfate with long-chain alcohols, were examined by microscopy, particle-size analysis, continuous shear rheometry, and creep (407, 408). The rheological properties of each emulsion were not directly related to particle-size distribution but to the nature of a gel network present in the continuous phase. Using very similar mixed emulsifier systems, Talman and Rowan (409–411) investigated the increase in consistency of o/w emulsions. The results indicated that for a fatty alcohol or acid in conjunction with the surfactant to have any self-bodying action in an emulsion, two conditions must be met: (*a*) a portion of the alcohol or acid must migrate from the oil to the aqueous phase, and (*b*) the surfactant molecules must be of such size and shape or be present in sufficient concentration to permit penetration of the amphiphile crystal lattice, thus forming a ternary liquid crystalline phase.

Other articles related to emulsions are presented in Table XI.

Ointments and Creams—New representations of the theoretical molecular concept of ointment structure was discussed by Huettenrauch (425). The concept included molecular order, molecular geometry, supermolecular structure, and total gel structure. The release, uptake, and permeation behavior of salicylic acid in ointment bases were investigated by Nakano and Patel (426). Release of salicylic acid from five ointment bases indicated that emulsion-type ointment bases are superior to oleaginous and polyethylene glycol ointment bases. The relative importance of the factors involved in the permeation of the drug from aqueous solution through ointment bases to another aqueous solution was studied with a three-compartment diffusion cell. The effect of adding aqueous solutions of methylcellulose to hydrophobic ointment bases on the diffu-

sion of salicylic acid was studied using an agar diffusion procedure (427). Enhanced diffusion of the acid from various ointment bases was observed. A study of the effect of polyhydric alcohols in ointment bases showed that the polyols had no effect on the release of sulfathiazole and salicylic acid (428). For long-term storage of the ointment bases, glycerol and sorbitol were the best humectants, and propylene glycol tended to reverse the emulsion type. The use of polyethylene glycols as an ointment base, combined with hydroxypropylmethylcellulose and water, was tested in model preparations (429). The viscosity, flow point, and cloud point of the compositions decreased and the medication release rate increased as the proportion of the hydroxypropylmethylcellulose–water hydrogel in the compositions increased. Tertiary phosphoric acid esters of poly(ethylene oxide) fatty acid alcohol esters, as used in washable dermatological ointments, were investigated (430). The lauryl derivative, in liquid petrolatum solutions, took up water in almost equal proportions to the ester concentration without becoming turbid.

The addition of hydrogenated lanolin or propylene glycol to a mineral oil base containing β-methasone-17-valerate or 21-deoxy-β-methasone-17-propionate markedly increased the vasoconstrictor potency of the valerate but not of the propionate (431). Two *in vitro* model systems for the study of the release of valerate from various vehicles were described. It was found that prednisolone in creams undergoes undesirable crystal growth to form the stable crystalline prednisolone hydrate (432). When the hydrate was used in the cream, no crystal growth occurred. Ointments containing promethazine hydrochloride, pheniramine *p*-aminosalicylate, and chloropyramine all showed some degree of photolytic and oxidative degradation (433, 434). The least change was noted in a water-free simple ointment. The use of some antioxidants was also shown to be of value. The effects of radiosterilization on the physical, chemical, and biological properties of ophthalmic ointments containing hydrocortisone acetate or chloramphenicol were reported in a series of articles (435–437). The use of γ-rays for the sterilization of these ointments appeared satisfactory. Degradation of liquid petrolatum by *Mycobacterium rhodochrous* was reported by Myers and Leslie (438). These findings were discussed with respect to drug and cosmetic preparations containing liquid petrolatum.

Other articles of interest relating to ointments and creams are listed in Table XII.

Table XII—Additional References on Ointments and Creams

Reference	Topic
439	Study of suspending agents used in calamine lotion
440	Evaluation of new emulsifiers for ointments
441	Evaluation of stickiness as a sensory test of rheological properties of w/o type cosmetic creams
442	Characterization and evaluation of bone fat as an ingredient of ointment bases
443	Apparatus useful in surveying drug release from ointments
444	Rheological and spectroscopic investigation of ointment bases
445	Review of preparation of cream emulsions
446	Observations on suspension stability of boric acid ointments
447	Observations of particle-size change in yellow mercuric oxide eye ointments with aging

Suppositories—The value of rheological measurements for the characterization of suppository vehicles was comprehensively investigated (448). Such measurements were found useful as criteria for evaluation of lipophilic suppository vehicles. The results obtained confirmed the colloidal character of lipophilic vehicles used in the production of suppositories. Medicament release from fatty suppository bases was related inversely to the consistency of mixtures of cocoa butter with different fats in terms of the viscosity index (449). Comparative *in vitro* investigations on the release of sodium chloride from water-in-oil suppository bases showed that surface-active agents with increasing HLB values result in increasing release of the sodium chloride (450). The *in vitro* release of active ingredients from triglyceride base suppositories was investigated. The release of materials such as codeine base, carbostyrylsulfonic acid, and aminophenazone, soluble both in fat and water, occurred according to their distribution coefficients in the different phases (451).

Hardness of suppositories based on various lipophilic substances was examined as a measure of the mechanical stability of the suppositories (452). Generally, the hardness of suppositories prepared and stored at 24° decreased with time. Those containing glyceride-type bases had the greatest hardness immediately after preparation. A spreading test was described for estimating the change in physical–chemical characteristics of suppository bases due to aging (453). This spreading effect was decreased by aging. From the biopharmaceutical viewpoint, it was pointed out that as high as possible a spreading effect is desired to obtain optimum drug liberation. The relation between artificial aging of lyophilic suppositorial vehicles and the time of full deformation of the suppository was investigated (454). The most pronounced changes were observed in suppositories prepared from aged cocoa butter; these underwent full deformation in 40% less time than those prepared from nonaged vehicles.

Xerogel dosage forms, prepared by lyophilizing frozen hydrogels of various shapes, were tested for their suitability for rectal administration (455). In addition to their chemical and physical stability, these new classes of xerogel dosage forms showed advantageous properties for application in body orifices with poor liquid supply. Polytetrafluoroethylene coating

Table XIII—Additional References on Suppositories

Reference	Topic
457	Release of diazepam from suppositories
458	Solubilization of drugs in suppositories of hydrosoluble bases
459	Two-layer suppository with a gelatin–glycerol base
460	Biological efficacy of camphor and strophanthin in two-layer suppositories
461	Stability of aminophylline suppositories designed for warm climates
462	Characterization of colored degradation products from aminopyrine suppositories

as a suppository mold-releasing agent was examined (456). It was found most effective on the release of fatty base suppositories, particularly from damaged molds, but had little effect on polyethylene glycol suppositories.

Further articles of interest on suppositories are presented in Table XIII.

Aerosols—Many papers were published during the past year reviewing the theoretical principles and technological development of aerosol systems (463–473). These papers discussed the operating parameters of aerosol systems, typical aerosol formulations and methods for evaluating them, and the numerous uses of aerosol products. The stabilization of aerosol emulsions and foams was considered by Sanders (474). The hypothesis was advanced that the interfacial region around propellant droplets in aerosol emulsions stabilized with molecular complexes is polymolecular and that the molecular complex has a liquid-crystal structure, almost insoluble in either the propellant or aqueous phase, which concentrates at the interface and stabilizes the emulsion by forming essentially a solid interfacial film. The evidence that molecular complexes have liquid-crystal structures in aqueous systems and that almost all aerosol emulsions and foam stabilizers are practically insoluble in both aqueous and propellant phases was the basis given for this hypothesis.

The release of ingredients from aerosols containing selected film-forming agents was examined, using gentian violet as a model substance (475). As the polarity of the film decreased, the rate of release increased; this release from the films studied followed first-order kinetics. Hardness and tackiness of various film formers of hair sprays were studied with the aid of a pendulum hardness tester (476). The results suggested that not only moisture but also sebum, plasticizer, and fragrance can exert important effects on the hardness of hair spray film formers. The effect of the size and ratio of valve body orifice to vapor tap orifice on fractionation of propellant and concentrate in cosmetic aerosol formulations was examined (477). On the basis of the results, it was recommended that the discharge rate for cosmetic aerosols be reduced by restricting the actuator orifice rather than the valve body orifice.

A method of evaluating the amount of corrosive acidity released by a given lot of anhydrous ethanol in admixture with a hydrolizable chlorofluorocarbon aerosol propellant was developed (478). Application of the test to undenatured alcohol samples from various sources showed that they differ in the degree of chemical stability as applied to aerosol formulations.

Sustained Release—Several articles were published dealing with the theory and practice of preparing sustained-release dosage forms (479–481). Equations were presented by Robinson and Eriksen (482) to allow calculation of doses and dosing interval for multiple-dose therapy of sustained-release dosage forms. Use of the appropriate equations yielded relatively uniform blood levels of drug. A stable sustained-action suspension of dextromethorphan as a hydrate was prepared by coating crystals of a poorly water-soluble salt of dextromethorphan in a solid particle-coating device with a triglyceride fatty acid mixture and dispersing the coated crystals in an aqueous vehicle (483). Great differences in physical and release-rate stability were observed with the same salt when it was coated by different methods or crystallized from different solvent systems.

The method of bead polymerization in the aqueous phase was intensively investigated to show the applicability for embedding drugs in polymers as a sustained-release dosage form (484). The presence of drug, either soluble or insoluble in the outer aqueous phase, decreased the bead size and yield of the products; the amount of drug which could be embedded in the beads depended on the affinity and solubility of the drug for the monomers. Nylon-encapsulated sodium pentobarbital, prepared by emulsion polymerization, was shown to exhibit a considerable reduction in dissolution rates compared with the instantaneously soluble forms (485). The release rate of sodium pentobarbital from the tableted microcapsular material was observed to be inversely proportional to tablet hardness. *In vitro* release tests indicated the sustained-release properties of a number of drug formulations (486–489), many of which exhibited *in vivo* effects as well. The diffusion of various progestational steroids through capsules or chambers of silastic rubber was investigated by several authors (490, 491). Both *in vitro* and *in vivo* release rates from this type of a sustained-action dosage form were determined. In *in vitro* experiments with human plasma as the incubation medium, less steroids were resorbed in a 24-hr. period than under *in vivo* conditions. Diffusion of the steroids through the siloxane rubber depended on the solubility of the steroid in the surrounding medium. The release rate of steroid implanted in the uteri of human volunteers was found to be proportional to the capsule length and was related, but not proportional, to capsule thickness. Permeation of steroids through dimethylpolysiloxane rubber film of various thicknesses and areas was shown to follow Fick's law (492). From these data, permeability constants were calculated and used to estimate the amounts of steroids diffusing from cylindrical implants. In another study, the permeability of three types of silicone rubber to steroids was examined (493). Permeation of the steroids through the polysiloxane membranes was inversely proportional to the number of hydroxyl groups present. Dissolution of steroids from lipid pellets of various compositions was determined as a measure of sustained release (494). Values obtained in these *in vitro* studies indicated that, after an initial period, the dissolution was constant.

Other articles related to sustained release are listed in Table XIV.

Cosmetics—Many problems in cosmetic chemistry during the 1960's received much clarification by the application of conformational analysis (505). General areas reviewed were proteins, enzymes, hormones, allergy, permeability, aging, the skin and its appendages, pigmentation, antimicrobials, olfaction, and taste. Factors influencing the design and formulation of dermatological preparations were ably reviewed by Wurster (506). Justification of the use of vitamins in cosmetic preparations for external application was presented,

along with a number of recipes for such preparations (507). The magnesium salt of ascorbic acid 3-phosphate was found to be suitable in various dermatological and cosmetic uses (508). In topical therapy, the phosphate was hydrolyzed by a phosphatase of the skin to release the vitamin C activity.

The use of esters of branched-chain aliphatic fatty acids and fatty alcohols, which tend to make a cosmetic film more porous and thus allowing carbon dioxide to escape, was proposed for cosmetic formulations as a necessary improvement for skin respiration and vitality (509). A review of recent studies emphasized the need for careful design and complete testing of suntan preparations (510). Use of a solar simulator to produce erythema was described for the evaluation of various sunscreen preparations on guinea pigs, both with and without washing after application (511). In most cases, rinsing the sunscreen sites with water destroyed most of the protection. The physiological mechanism of perspiration and the effect of aluminum compounds as active compounds in antiperspirants were discussed (512). Recipes for use in various cosmetic preparations were also described. A study of aminothio ethers, such as *S*-benzylcysteamine malate, leading to interesting antiseborrheic formulations and cosmetic applications was described as a possible future development in the field of acne (513). The adherence of two vegetable oils and mineral oil to keratin was studied in a bath oil preparation at a 0.02% concentration. Results indicated that not only does more vegatable oil than mineral oil adhere to keratin, but a substantial amount of oil also appears to bind more tightly to the keratin (514). The use of pigments in cosmetic preparations and their coloring and toxicological properties were also reviewed (515). Modern perfume oil dosing in various cosmetic formulations ranged in quantities from 12–15% in aerosol perfumes to 0.3–0.5% in vanishing, face, and cleansing creams (516). Isopropyl myristate was recommended as a useful adjunct in most fluid formulations.

The use of a surface-active powder, developed from methylolurea, as a highly acceptable fabric-free cover for wounds was reported (517). Besides its use in medicine, this powder can be used in the cosmetic industry as a face, body, shaving, and foot powder or as a powder to stop bleeding. The properties and characteristics of a new cosmetic material were described (518). The advantages of this cosmetic ingredient were shown in typical formulations. A practical guide to gums and thickeners available for use in cosmetic formulations was presented by Young (519). Factors involved in producing stable products were also considered.

In a discussion of sanitation in cosmetic manufacturing, it was emphasized that a cosmetic producer must do everything he can to maintain the most stringent conditions in all aspects of manufacturing, packaging, and distribution (520). An investigation of ethylene oxide treatment of large volumes of various cosmetic ingredients demonstrated a great reduction of microorganisms in the dry ingredients (521). Dry organic materials as well as inorganic materials were favorably affected by this treatment. Various aspects

Table XIV—Additional References on Sustained Release

Reference	Topic
495	Use of glycerol palmitostearate for preparing sustained-release tablets according to embedding principle
496	Delayed-action dosage forms of chlorpromazine
497	Medicinal preparations of prolonged action
498	Preparation of sustained-release capsules by coating small tablets made by compression
499	Sustained-release tablets of cycloserine
500	Investigations of a new timed-release dosage form of propoxyphene hydrochloride
501	Sustained-release tablets with stearic acid
502	Hydrophilic gels in preparation of sustained-release tablets of ammonium chloride
503	Long-acting form of methacycline
504	Timed-release ascorbic acid capsule

of preservative failures in cosmetics resulting in microbiological spoilage were ably reviewed in several articles (522–524). The necessity for adequate preservative systems was emphasized. During the year, Gucklhorn (525–534) continued the comprehensive survey of the advantages and disadvantages of the various preservatives used in cosmetic preparations, including the updating of information on materials previously reviewed. Allergic skin reactions from cosmetic preservatives were surveyed (535). False negative allergy tests to parabens, sorbic acid, and other preservatives were reported to be prevalent when patch tests were made using the cosmetic cream or lotion supplied by the manufacturer.

In other reviews, the use of ethyl and isopropyl alcohols and other compounds that slowly release formaldehyde were considered as preservatives in cosmetic formulations (536, 537). Although the preservative action of phenylmercuric salts at 0.005–0.01% concentration was almost completely neutralized by compounds containing sulfhydryl groups, Eckardt (538) demonstrated that 2% solutions of keratin can be preserved with phenylmercuric acetate, and that the preservative activity can be improved by the addition of sodium lauryl sulfate. For the stabilization of hydrophilic bases used in cosmetic preparations, a binary preservative system composed of 0.01% hexachlorophene and one other preservative, such as 0.2% methylparaben or 0.1% benzyl alcohol, was recommended (539). Although products containing protein hydrolysates are relatively difficult to preserve, tests with 2-bromo-2-nitro-1,3-propanediol indicated it was a powerful, nontoxic preservative which was not affected by the large amounts of protein found in shampoos, rinses, conditioners, and creams (540). A new family of antimicrobial preservatives for cosmetics was described based on the development of a series of substituted imidazolidinyl urea compounds (541).

Packaging—The current status of single-unit packaging of medications was discussed in regard to the need for the availability of this package for many commonly used drugs in hospitals (542). Lists of currently available medications in single-unit packages were also presented. Drug–plastic considerations for use of plastics in packaging parenterals were reviewed by Autian (543) and included permeation, leaching, sorption, chemical reactions, and stability of the

Table XV—Additional References on Packaging

Reference	Topic
552	Packaging of compositions containing acetylsalicylic acid
553	Comparative analytical study of pharmaceutical glass containers in the establishment of Columbian National Standards
554	Release of additives from pharmaceutical containers made from polyvinyl chloride
555	Performance tests for plastic containers
556	Evaluation of extraction tests for plastics
557	Chemical resistance of carbamide plastic used for ointment containers
558	Stability of aluminum foil-sealed cycloserine capsules

materials. The sorption of *p*-hydroxybenzoic acid esters, phenols, and other preservatives by plastic materials such as poly(methyl methacrylate), polyethylene, and polyvinyl chloride were investigated by several authors (544–546). The degree of sorption apparently depended on the structure of the compound. A study of the sorption of *p*-hydroxybenzoic acid esters by capran polyamide showed that the *in vitro* biological activity of the parabens in the presence of the nylon was related to the concentration of drug in equilibrium with the plastic (547).

A procedure was proposed by which it is possible to predict, with reasonable accuracy, the change in concentration that occurs during the autoclaving of solutions in polyethylene containers (548). The prediction was based on the assumption that permeation is related to partitioning of the solute between the water and the polyethylene. Polyethylene and polypropylene containers were found to be satisfactorily inert and did not affect the stability of a 5% aqueous glucose solution; the polyvinyl chloride container was satisfactory due to the effect of an extracted plasticizer (549). Storage tests with an alcoholic camomile extract in different plastic containers indicated that high and low pressure polyethylene containers exhibited loss of chamazulene and etheric oil due to absorption into the container walls (550). No absorption was detected in the rigid polyvinyl chloride or polypropylene containers. In similar studies, the stability of eight plasma-substitute solutions in various plastic containers was investigated (551). After storage for 1 year under normal conditions, the solutions changed little in physicochemical properties aside from changes in pH.

Other articles related to packaging are described in Table XV.

Equipment—Progress in pharmaceutical engineering was reviewed by Fowler (559). The engineering aspects of size reduction, particle-size measurement or characterization, drum mixer, solids handling, and granulation were discussed. Another review discussed the advantages and applications of different systems of laminar flow and clean rooms (560). The use of Torit dust collectors on tablet compressors and mixers and in granulating areas was described (561). The main use was in product and personnel protection, but an occasional advantage was the recovery of an expensive drug. Engineering aspects of the flow of particulate materials from hoppers were presented by Miles (562). Some methods and devices for overcoming practical problems that arise from mass flow hopper design were considered, together with problems involved in designing accurate feeding systems. A description of the Marumerizer and the associated extruder, together with operating experience in the manufacture of small solid pharmaceutical spheres, was presented (563, 564). The spherical particles produced were shown to have advantages of regularity and shape, consistency of size, and definite surface characteristics in comparison with spherical or granular particles produced by other means. A general study of the technology for using a solids processer (a vacuum tumble dryer) was made to evaluate the overall applicability to the processing of pharmaceutical granulations (565). Experiments on mixing, drying, formulation factors, and processing factors were recorded.

PHYSICAL PHARMACY

The existence of six different polymorphic forms of aspirin (two of which were known) was determined by differential scanning calorimetry, hot-stage microscopy, and true density measurements (566). The thermal behaviors of four crystalline forms of sulfanilamide and of sulfanilamide-d_4 were examined, and heats of transition and fusion were determined. The deuterated modifications exhibited smaller heats of transition and heats of fusion than the corresponding undeuterated forms (567). Through a systematic investigation of the crystallization of cephaloglycin and cephalexin, a better understanding was obtained of the part that pseudopolymorphic crystal transitions play in the analysis, processing, and formulation of these compounds. A convenient and sensitive method for detecting new crystalline phases was reported which employed solubility *versus* solvent composition diagrams to detect various crystal forms of compounds. This method should find application whenever crystallizations are performed with more than one solvent and, particularly, when the instability of the compound at elevated temperatures prevents the use of conventional thermal methods or when poor crystal development limits the use of microscopic methods (568). Two polymorphic forms and a hydrate of an investigational compound were reported in which no appreciable difference in the dissolution rate was detected for the various forms in artificial gastric fluid. Dissolution studies in water indicated the formation of a hydrate, and protective colloids were shown to have an effect on the hydrate formation. In particular, methylcellulose slowed down the rate of crystal growth of Form I significantly (569). Shenouda (570) described a crystallized sulfathiazole form which consisted of varying proportions of a melting species and another species that underwent solid–solid transition. Grinding appeared to destroy the melting species and to have a significant effect on the transition temperature but not on the heat of transition. Three crystal modifications of chlordiazepoxide hydrochloride were described: a stable form, a hygroscopic form, and a monohydrate (571).

It was noted that permeability of most doublelayer films has a directional property and they can be made thinner than single films, suggesting their potential

usefulness in the manufacturing process of pharmaceuticals that are water unstable and require rapid disintegration (572). Most combinations of coating films showed "two-sided" permeability; this property was not previously reported for films composed of hydrophobic layers only. It was found that in double-layer films with "two sidedness," there is a characteristic relationship between the specificity of permeability and the humidity range (573). Since the moisture permeability of most double-layer films has a directional property, this two sidedness may be brought about mainly by a change in the permeability coefficient as a result of a change in vapor pressure (574).

Herzog and Swarbrick (575) described the development of a polymeric nonporous model membrane containing natural membrane components and its use in a two-compartment transport cell. A standard model biomembrane was designed containing 44% ethylcellulose, 44% biological materials, and 12% mineral oil. From the lack of solvent flux under experimental conditions and the first-order disappearance of salicylic acid, it appeared that the polymer membrane mimicked the functionality of natural membranes insofar as passive diffusion was concerned. A theoretical equation was developed justifying the graphical representation of vapor permeation data by 1/rate *versus* film thickness plots. The permeability coefficient for the film could be determined from the slope of the plot and had units in square centimeters per second, while the intercept at zero film thickness was dependent upon the geometry of the experimental design and the diffusion coefficient for the vapor within the diffusion cell (576). Films composed of poly(methylvinylether)-maleic anhydride copolymer, crosslinked with polysorbate 20, appeared as the most promising of the systems studied for film-controlled drug-release application. The permeability of the films could be controlled by adjusting their polysorbate 20 content and the molecular weight of the polymer and by humidity pretreatment. The permeability of the films was affected also by the pH of the diffusion medium (577). A system of molecular scale drug entrapment was developed, which provided a physicochemical and highly reproducible method of effecting drug entrapment and subsequent controlled drug release from polymeric matrixes. The flocculation of highly concentrated colloidal polymeric dispersions (latexes), in the presence of the drug in solution which is to be occluded, provides the entrapment mechanism. A significant increased duration of action and a reduction of the acute toxicity of methapyrilene in the entrapped form were established by *in vivo* effectiveness studies. The broad application of the entrapment process to acid salts of 11 widely used cationic nitrogen-containing drugs was demonstrated (578). It was shown that a suitable organic acid greatly increased the degree of interaction between the drug and the polymer and provided a mechanism in controlling both interaction and subsequent drug-release properties. *In vitro* tests indicated that the products obtained by this technique could be used in either solid or liquid dosage forms (579).

Further studies on the facilitated molecular scale entrapment technique for preparation of controlled-release pharmaceuticals were reported, including *in vitro* and *in vivo* tests of phenylephrine and phenylpropanolamine products obtained by the facilitated molecular entrapment method. This testing indicated that the process possesses considerable potential for exploitation of the sustained-action or controlled-release pharmaceutical dosage form (580).

The *in vitro* dissolution patterns of some spray-congealed products of sulfaethylthiadiazole–wax made into compressed tablets were reported. The mechanism of release of sulfaethylthiadiazole appeared to be due to erosion, solubilization, and leaching of the drug from the tablet. The Higuchi model for drug release from inert matrixes could describe the release pattern for only the initial few hours when, apparently, variables other than amount of drug released and time were essentially constant (581). The *in vitro* release behavior of chloramphenicol from four different bead polymers containing methyl methacrylate and α-methacrylic acid in various buffer solutions was studied. The concentration of α-methacrylic acid in the copolymer beads and the pH and ionic strength of the buffer solutions influenced the release rate of chloramphenicol from these beads. The beads containing no α-methacrylic acid did not release the drug in any buffer solution, and the beads containing only α-methacrylic acid released the drug at almost the same rate in all buffer solutions (582).

McGee *et al.* (583) reported on some of the factors affecting release and availability of aspirin, aspirin and lactose, and aspirin and dibasic calcium phosphate mixtures from hard gelatin capsules. Significantly better plasma levels were obtained with the more tightly compacted No. 4 capsules, as opposed to the same formula administered in a No. 3 hard gelatin capsule. This possibly was due to the diffusion of gastric juice through the gelatin, which created higher pressure within the capsules. A direct correlation of *in vitro* dissolution data and *in vivo* plasma level data could not be made. In a similar study, the effect of particle size and packing on the *in vitro* release of a water-insoluble hydrophobic drug from hard gelatin capsules was related to the liquid permeability of powder beds of similar porosities. Drug release and permeability decrease with a decrease in particle size and porosity of the powder bed. A moist granulation process transforms a nonpermeable powder bed, which allows low drug release, into one with high permeability and high drug release (584).

The *in vitro* release of medroxyprogesterone acetate from a silicone rubber matrix was studied, and a nonlinear dependence of release rate upon drug concentration within the matrix was found. Based upon a model system, equations were derived to explain this behavior and to include other parameters that may influence the release rate. The study suggested that the partition coefficient, diffusion coefficients, the medroxyprogesterone acetate concentration within the polymer, and agitation conditions play important roles in the release process (585).

The transport kinetics of salicylic acid was studied in an *in vitro* model cell containing two aqueous phases separated by a third liquid–lipid phase simulating

Table XVI—Additional References on Physical Pharmacy

Reference	Topic
596	Distribution of tetracycline antibiotics in two-phase systems
597	Characterization of the form of lactose in spray-dried lactose to show existence of α-monohydrate and α- and β-anhydrous forms
598	Review of pharmacogenetics with special emphasis on polymorphism
599	Model of a membrane structure and the basic principles of solute transport through dialysis membranes
600	Influence of some aliphatic and steroid alcohols on liberation rate of citric acid from petrolatum
601	Acid dissociation constants and zwitterionic character of 2-aminoethaneselenol
602	Review of very fine particles, including properties in the dry state and in liquids

the biomembrane. The rate constant for the transport of salicylic acid from the aqueous phase to the lipid phase always increased with increased polarity of the lipid phase; however, the transport of the drug from the lipid phase to the second aqueous phase increased or decreased, depending on the stirring condition employed in the two aqueous phases (586). The effect of surfactants on the diffusion of testosterone through cellulose acetate membranes was studied in an attempt to determine the possible mechanisms by which surfactants may affect drug transport. In all cases examined, the surfactants reduced the diffusion coefficient of testosterone (587).

By using NMR data, the hydrophobic bond-weakening effect of urea on *d*-propoxyphene hydrochloride self-association was demonstrated (588). In studying the formation of mixed ligand chelates containing penicillamine and sulfhydryl compounds, Sugiura and his coworkers (589, 590) concluded that the formation constants of mixed ligand chelates are linearly correlated with the dissociation constants of the sulfhydryl group in secondary ligands. Among the mixed ligands studied, the decrease in binding affinity of the carboxyl group in penicillamine tended to increase the formation of the mixed ligand chelate.

X-ray crystallographic procedures demonstrated that the structures of *erythro-* and *threo-α,β*-dimethylacetylcholine iodides were substantially different in conformation in that the *threo*-compound appeared to be dominated by coulombic attraction between the carbonyl oxygen and the quaternary nitrogen group. In the *erythro*-analog, the acyloxy oxygen atom was involved in a similar intramolecular interaction (591).

The effect of pH of precipitation on the physical and chemical properties of hydrous aluminum oxide was studied. During aging, changes may occur in the hydrous aluminum oxide structure which result in a loss in antacid reactivity; this loss follows apparent first-order kinetics. The rate of loss was directly dependent on the pH of precipitation and continued until a constant end-point was reached. The percentage of theoretical reactivity remaining at the end-point was inversely related to the pH of precipitation. While no differences in form were detected by X-ray diffraction, either initially or during aging, gel stability appeared to depend on the presence of anions in the gel structure; the concentration of these anions was related to the pH of precipitation. Data were presented which demonstrated that a stable, completely acid-reactive gel can be obtained if 1 mole of a monovalent anion or 0.5 mole of a bivalent anion is incorporated in the gel structure per mole of aluminum (592).

The effect of charge shielding by nonpolar groups on the partitioning of quaternized amines was studied by comparing a series of 2,6- *versus* 3,5-methyl-substituted *N*-methylpiperidine methiodides. There was little difference in their partition coefficients (593). The apparent partition coefficients of chlorpromazine and some other phenothiazine derivatives in dodecane–water and *n*-octanol–water systems were measured at 30°. Only the free base formed partitions in the dodecane system at various pH values. Intrinsic partition coefficients for all derivatives, except the very polar chlorpromazine sulfoxide metabolite, ranged from 10^4 to 10^5, indicating the remarkable hydrophobicity of these molecules. Partitioning measurements in *n*-octanol indicated significant extraction of these drugs as ion pairs, as well as higher intrinsic partition coefficients than in dodecane. From this work, it was shown that quantitative studies involving the phenothiazines in heterogeneous systems, such as membranes, must consider the extreme hydrophobicity of these compounds and the various factors that influence such behavior (594). A mathematical model was derived which permitted a quantitative evaluation of salt effects in urea–drug solutions. The theoretical calculations, based on this model, were in good agreement with the experimental values observed for neutral and pH 1 solutions of methylsalicylate and methylbenzoate in urea. Significant error in interpretation of solubility in urea may result if these salt effects are disregarded (595).

Additional references on physical pharmacy are provided in Table XVI.

Dissolution—When a commercial tablet was converted to a capsule dosage form for purposes of conducting a double-blind clinical trial, the *in vitro* dissolution times of the drugs from the capsule were strikingly prolonged. Various capsule adjuncts were examined in an attempt to decrease dissolution times of drugs from capsules. Of the series tested, lyophilized glycine had the best positive effect in shortening the dissolution times of all drugs examined (603). In studying the *in vitro* dissolution behavior of several experimental capsule formulations, it was demonstrated that the capsule lubricant magnesium stearate and the filler lactose or dibasic calcium phosphate dihydrate had the greatest influence on the disintegrations of the capsules. It was noted that drug dissolution was limited by the rate of erosion, diffusion, and/or solution of the drug and/or filler from the wet powder mass that was characteristic of slow dissolving formulations. The data suggested that the high viscosities of several of the powder packs were due to their restricted water content arising from the added hydrophobic lubricant (604). Relatively insoluble drugs formulated in soft elastic capsules were released faster than from commercially available tablets due to the more rapid dispersion of the active ingredients, which is enhanced by the use of solubilizers

and/or surfactants in the formulation. Soft elastic capsules were recommended for the formulation of low-dose medications of relatively insoluble drugs and drugs for which an early high-blood level of the drug is indicated (605).

The influence of a nonionic surface-active agent on the dissolution rate of benzoic and salicylic acids was investigated, and the dissolution mechanisms were examined as a function of the hydrodynamics of the system. The dissolution rate of a solid in a micellar solution was not proportional to the solubility of the compound in the dissolution medium. Evaluation of dissolution-rate data and theories led to the conclusion that, depending upon hydrodynamic conditions, the dissolution rate of a solid will be proportional to the effective diffusion coefficient raised to a power between 0.5 and 1.0 (606). At a very low concentration of FD&C Blue No. 1, a remarkable inhibition of dissolution was observed for single crystals of sulfathiazole, phenobarbital, thymol, and sulfaguanidine under controlled conditions. Data presented agree with the current theories concerning dissolution inhibition by small concentrations of impurities and suggest that the dye molecules are preferentially absorbed at the primary dissolution sources in the crystals investigated (607).

A three-compartment apparatus was developed for dissolution studies of slightly soluble powders under sink conditions. The apparatus could accommodate a barrier in the dissolution medium which prevented floating powders from entering and dissolving directly in the sink phase. Dissolution studies were conducted with several particle-size grades of salicylic acid under nonsink as well as sink conditions. The data indicated that with a diffusion-controlled rate of agitation, using appropriately placed propellers, it was possible to establish a rank order for *in vitro* dissolution times of different particle-size salicylic acid powders (608). An apparatus for the study of dissolution rate under conditions of continuous flow was described. Typical data were presented, demonstrating the major advantages of this method over present methods to be the following: (*a*) has greater flexibility, (*b*) produces data in a differential form, (*c*) utilizes a small volume system which assures greater homogeneity, and (*d*) prevents excessive accumulation of solute in the system and provides agitation and solvent flow in a controlled, measurable, and physically meaningful manner (609).

In a study of the influence of pulsation on the dissolution-rate measurements in column-type apparatus, it was recommended that for dissolution tests in flow-through methods, momentum pumps should be used instead of displacement pumps so that results found at different times in different laboratories can be compared (610). The dissolution of aspirin from different commercial dosage forms was evaluated by the rotating-flask method and the data were correlated with previously recorded absorption data. The dissolution rates in descending order were: buffered tablets > plain tablets > timed-release tablets. Aspirin dissolved from the buffered tablet about twice as rapidly as from the plain tablet and about eight times as rapidly as from the timed-release tablet. However, once disintegration and deaggregation took place, the dissolution of aspirin from the capsule formulation proceeded as rapidly as from the buffered tablet. Excellent single- and multiple-quantitative correlations were observed between the dissolution data and absorption data in man (611).

An investigation was conducted to analyze the dissolution behavior of a poorly water-soluble drug. Two specific methods of micronization were employed which provided drug forms of different physical characteristics, specific surface area, and particle-size range. The drug was micronized by employing spray drying and air attrition. The micron-sized drugs, pelletized pure drugs, and tablets prepared from each of these by direct compaction were subjected to dissolution-rate studies at pH 1.2 and 3. The *in vitro* dissolution data obtained demonstrated a significant variation for the pure spray-dried and air-attritioned drugs at pH 1.2, although physical specifications had suggested the contrary of that reported. When the pure drug forms were pelletized, the difference observed in the dissolution rates with the pure drug powders was eliminated. Dilution of the pure drug with tablet excipients and the subsequent direct compaction into tablets improved dissolution behavior compared with that obtained with the pure drug forms (612). The dissolution rates of phenobarbital, sodium phenobarbital, phenacetin, and prednisolone in human gastric juice were investigated. The rate of dissolution of phenobarbital from tablets prepared with gelatin as a granulating agent increased with decreasing particle size of the drug. Phenobarbital from the same tablets dissolved much faster in human gastric juice than it did from tablets prepared with sodium carboxymethylcellulose or polyethylene glycol 6000. The rate of dissolution of sodium phenobarbital in human gastric juice and in 0.1 *N* HCl was lowered by granulating a mixture of the drug and potato starch with gelatin. Compressing these granules into tablets further reduced the dissolution rate (613). Adding polysorbate 80 caused an increase in the dissolution rate of acetylsalicylic acid in 0.1 *N* HCl when the particle size of the drug was relatively small. If the particle size was larger (0.7–1.0 mm.), polysorbate 80 had no accelerating influence on the dissolution rate. This difference in the effect of the surfactant may be due to the fact that the hydrophobic properties of aspirin are so insignificant that a reduction of the surface tension between drug and liquid is of importance only when the drug's specific surface is large, *i.e.*, when the particle size is small (614).

Using a polyethylene maleic anhydride–phenylpropanolamine interaction system as a model, Heyd (615) showed that the preparation temperature of the polymer–drug has a pronounced effect on some physical–chemical properties of the polymer–drug system relative to dissolution of the drug. Factors influencing the dissolution of an ethylene–maleic acid copolymer were studied. Swelling, hydrated layer thickness, and solvent pH influenced the dissolution of the polymer. Linear dissolution rates were observed following an initial induction period, and hydrated layer thickness was a controlling factor in the dissolution process (616). Using the rotating-disk method, the dissolution

Table XVII—Additional References on Dissolution

Reference	Topic
619	Review including discussions of rates of disintegration and dissolution processes, methods of determining disintegration time *in vivo* and *in vitro*, and relations between disintegration time and physiological availability
620	Chronological bibliography on rate of dissolution of pharmaceuticals *in vitro* and *in vivo*
621	Review of historical highlights in development of rate of dissolution of drugs *in vitro* and *in vivo*
622	Theoretical and descriptive review of methods of measuring and interpreting rates of dissolution of pure compounds
623	Correlations of percent drug released *in vitro* with *in vivo* availability for various drugs
624	Differences in rate at which ferrous sulfate is released from various tablet formulations attributed to chemical reactions occurring between ferrous sulfate and other ingredients in the tablet
625	Review of intradependency of factors affecting dissolution rate, uniform dissolution-rate tests, and interpretation of dissolution-rate data, including surface area and kinetic studies
626	Influence of granulation method on the dissolution rate from tablets and tablet granules, showing significance when finely ground drug was used
627	Laboratory experiment in pharmaceutics, showing the influence of pH and agitation intensity on dissolution rate of salicylic acid
628	Influence of particle size and other technological factors on absorption and *in vitro* dissolution rate of phenytoin from tablets
629	Effect of compression force and additives in tableting on tablet dissolution *in vitro* and *in vivo*

of polyvinylpyrrolidone was investigated in an acetone–water system. Three dissolution stages were observed: the initial stage involved swelling, which induced dissolution, and the final stage involved coacervation of polyvinylpyrrolidone. When sodium chloride was added in bulk solution, the initial stage seemed unessential, and the whole dissolution rate increased. This was considered due to a suppression of the swelling of polyvinylpyrrolidone on the surface of the disk by the adsorption of sodium on polyvinylpyrrolidone (617). Similar dissolution studies of fractionated polyvinylpyrrolidone were conducted. Again, three stages of dissolution were observed; the initial stage was shortened and there was a decrease in molecular weight. The main stage was expressed as a function of the molecular weight of polyvinylpyrrolidone and the absolute temperature (618).

Additional studies on dissolution are listed in Table XVII.

Solubility—Anhydrous and dihydrate forms of an aminoalicyclic penicillin were compared for solubility in distilled water at temperatures ranging from 7 to 60°. Below the transition temperature of 61°, the anhydrous form was significantly more soluble than the dihydrate. The solubility of the anhydrous crystal was inversely related to temperature. Thermodynamic properties for the two forms of the antibiotic were experimentally evaluated (630). In a solubility study of testosterone propionate, methyltestosterone, and 19-nortestosterone, oxycholate was a better solubilizer than the aqueous sodium cholate, and both bile salts solubilized more 19-nortestosterone than the other derivatives. A possible mode of solubilization was presented (631). Using a radioactive technique, it was shown that the *in vitro* solubility of cholesterol was greatly increased in the presence of acacia and pectin. This finding is in contrast to previous reports that acacia had no effect on feeding experiments (632).

Entropy considerations showed that solvent–solute interactions occur in some solvent–testosterone propionate systems that increased solubility, resulting in deviations from regular solution behavior. It was noted that regular solutions are obtained only in saturated hydrocarbon solvents, and that solubility can be more accurately predicted as the temperature approaches the melting point and as the molar volumes of solvent approach that of the solute (633). Ostrenga and Steinmetz (634) reported solubilities for two steroids and indicated that the fractional molar attraction constant may be a useful parameter for solubility estimations, since it relates the solubilizing capacity of solvents for a given steroid.

The need for caution in interpreting solubility phenomena involving cosolvent systems in general and urea–water systems in particular was reported (635). The solubility of dodecane increased as the concentration of aqueous solutions of formamide, *N*-methylformamide, and dimethylformamide increased. Positive values of standard free energy and negative values of enthalpy and entropy decreased numerically as the concentrations of amides increased (636).

The solubilities of eight physiologically active barbiturates were determined in binary mixtures of alcohol and water. The dielectric requirement of the barbiturates illustrated an approximate inverse relationship with the number of carbon atoms in the molecule. The onset of action after administration and the duration of action of these barbiturates increased as their relative polarities decreased. An approximate correlation between activity and solubility ratios was considered (637). The effect of the hydrophobic chain length of the polysorbates on the degree of solubilization of a series of 5,5-disubstituted barbituric acid derivatives was studied. The solubilities were increased as the hydrophobic chain length increased. The number of carbon atoms of the substituents on the 5-position, as well as their inductive effects, determined the extent of solubilization (638).

A similar study of the solubilities of barbituric acid derivatives in aqueous solutions of polyoxyethylene stearates of varying polyoxyethylene chain length was conducted. Except for phenobarbital, which formed an insoluble precipitate complex with all the solubilizers, all the other barbiturates studied were micellarly solubilized. On a molar basis, solubility increased with an increase in hydrophilic chain length but decreased if the solubility was expressed in terms of the amount solubilized per ethylene oxide unit. The partition coefficient of the drug molecules between a micellar pseudophase and an aqueous phase was dependent on both the polar effect and the number of carbon atoms of the substituents on the 5-position. The formation of an insoluble precipitate complex by phenobarbital was attributed to the presence of the aromatic phenyl group in the molecule (639).

The applicability of a new technique in solubilization, using a molecular sieve, was tested on a system consist-

ing of benzoic acid and cetromacrogol 1000 in aqueous solution. The data obtained were in good agreement with those found by other methods, and the advantages of the new technique were outlined (640). The solubility features of a homologous series of alkyl *p*-hydroxybenzoates with alkyl groups, in an ascending order from methyl to *n*-butyl, were investigated together with benzylparaben and methyl *p*-methoxybenzoate. A phenomenon of mutual solubilizing potential was observed to exist when the solubility of a mixture of an alkylparaben and benzylparaben in 60% polyethylene glycol 400–water was examined. The scope of application of these esters for their antimicrobial properties was envisioned to be augmented by considering factors influencing solubility (641).

Additional studies on solubility are listed in Table XVIII.

Complexation—The many publications dealing with complexation phenomena (interaction, binding, *etc.*) have been divided into two categories: interactions dealing with biological substances such as plasma proteins, and interactions dealing with nonbiological substances.

Interactions of Drugs with Biological Substances—Mefanic acid, ethacrynic acid, nalidixic acid, and diazoxide displaced significant amounts of warfarin from human albumin *in vitro* by a noncompetitive mechanism. If this occurred *in vivo*, the clinical use of these drugs would cause an increase of 66–400% in free active warfarin, and it would be necessary to reduce the dosage of anticoagulant to prevent excessive hypoprothrombinemia and hemorrhage (664). The binding of a series of conjugated bile salts and fatty acid salt anions to cholestyramine from aqueous media was investigated; affinity constants increased as the number of hydroxyl substitutents on the bile salt ring structure decreased. An increase in the chain length of the fatty acid salt caused a corresponding increase in the affinity constant, whereas an increase in the extent of unsaturation in the fatty acid chain produced a reduction in the affinity constants for the fatty acid–cholestyramine interaction. Based on these results, it was suggested that the binding mechanism involves a primary electrostatic component reinforced by a secondary nonelectrostatic interaction, the strength of the latter force being dependent on the degree of hydrophobicity of the adsorbate molecule (665).

The *in vitro* rate of binding of several conjugated bile salt anions to cholestyramine was studied at 27°, along with and in the presence of varying concentrations of sodium chloride. The temperature and agitation studies suggested that the binding of bile salt anions to cholestyramine apparently occurs by means of a diffusion-controlled process (666). The role of hydrophobic interactions in inhibiting the relatively specific enzymatic reactions of five enzyme systems by a series of congeneric drugs was illustrated by the use of substituent constants and regression analysis. The inhibition of certain enzymes by congeneric drugs was linearly dependent on the lipohydrophilic character of the inhibitors (log P or π). The inhibition of other enzymes by drugs was linearly dependent on the log P and Hammett's σ constant. For monoamine oxidase inhibition by substituted β-carbolines, a parabolic equation of log P gave the most significant correlation. The ideal lipohydrophilic character (log P_0) for maximum inhibition was 2.74 (667). The binding of *para*-substituted acetanilides to bovine serum albumin was examined at pH 7.2; an excellent correlation was obtained between the binding enthalpy and Hammett's substituent constant, σ. This was interpreted to mean that binding is nonspecific in nature. A very good correlation was also obtained between the entropy of binding and σ, which suggests that the extent of hydration of unbound drug is a function of the charge separation within the drug molecule (668).

More than 90% of the plasma content of chlorpromazine was bound to human plasma protein, the binding being affected by the pH of the aqueous medium. Variation in binding in plasma from different humans was marked (669). Campbell and Todrick

Table XVIII—Additional References on Solubility

Reference	Topic
642	Solubility of benzoic acid in aqueous solutions of monododecyl polyoxyalkanols
643	Effects of third component on hydrophobic and hydrophilic moieties of tryptophan in aqueous solution; approach to understanding the denaturation of globular protein
644	Effect of third component on water structure around tryptophan in aqueous solution
645	Properties of mixtures of glycols and their derivatives with water, indicating that association occurs in these mixtures
646	Association in water-solubilizing agent systems in which one substance possessed both hydrophobic and hydrophilic groups; lack of association in systems having only a hydrophilic group
647	Solubilization and emulsification of hexachlorophene using nonionic emulsifiers
648	Solubility of menadione in nonionic surfactants suggested by complexation
649	Relative pharmacologic activity of insulin-inducing sulfonylureas studied as a function of their water solubility
650	Solubility of testosterone in aqueous solutions of ionic surfactants using interference refractometry
651	Solubilization of therapeutically used arylamines by *n*-propylaminoacetylation
652	Solubilization of blasticidin *S*-benzylaminobenzenesulfonate by guanidine hydrochloride–nonionic surfactant solutions
653	Laboratory experiment showing characterization of a poorly soluble complex by a solubility method
654	Solubilization of purine alkaloids by polyvinylalcohol and suggested mechanisms
655	Solubilization of *N,N*-diethylaniline by trimethylcetylammonium bromide involving formation of a dimer within the elliptical micelle; solubilization of α-naphthylamine involving an adsorption–penetration mechanism followed by dimerization
656	Solubilization of reserpine by nonionic surfactants
657	Effect of polar substances on solubility behavior of anionic, cationic, and nonionic surfactants in nonpolar solvents
658	Solubility and hydrolysis rate of 1-monolaurin in aqueous solutions, including thermodynamic parameters
659	Temperature effect on solubility of tetracycline base–water–ethylene glycol system
660	Mechanism of solubilization of khellin by sodium benzoate and salicylate
661	Successive and simultaneous solubilizations of two different water-soluble dyes by surfactants
662	Solubilization of benzene and styrene in solutions of some ionic and nonionic surfactant mixtures
663	Effects of isomeric form and length of carbon chains on solubilization of various hydrocarbons and polar compounds

Table XIX—Additional References on Interactions of Drugs with Biological Substances

Reference	Topic
675	Binding of steroid conjugates to human corticosteroid-binding globulin
676	Kinetics of dialysis for certain drugs in the presence and absence of albumin, showing estimates of unbound and bound forms of the compound
677	Physiological implications of interactions of drugs with aspirin
678	Evaluation of *in vitro* enhancement of protein binding of certain organic acids and bases
679	Studies of an *in vitro* binding reaction between thyroid microsomes and long-acting thyroid stimulator globulin; development of solid-state competitive binding radioassay methods for measurement of antimicrosomal and antithyroglobulin antibodies
680	Binding of penicillins and serum protein
681	Nature of drug interactions for use by the practicing pharmacist
682	Ion binding of penicillins to proteins
683	Measurement of binding constants of phenylbutazone and oxyphenbutazone to proteins using circular dichroism
684	Lack of enhancement by myocardial contraction on binding affinity of digitalis glycosides to myocardial receptors
685	Hypothesis of a calcium chelating mechanism for caffeine action *in vivo*
686	Binding of a diphenhydramine analog to bovine serum albumin
687	NMR study of binding of aspirin to human serum albumin
688	Complexes of certain sulfa drugs with each other being better absorbed intestinally than individual sulfa drugs
689	Induced changes in plasma protein binding of methotrexate with salicylate or sulfisoxazole being useful in cancer therapy
690	Mechanism of metachromasy of 2,4′-hydroxyphenylazobenzoic acid by serum albumin
691	Interactions of cations and local anesthetics with phospholipids
692, 693	Statistical–mechanical model for binding of flexible ligands to protein with application to various ligand–surface systems
694	Preferential binding of dipyridamole to β-globulin in plasma rather than to albumins
695	Review of plasma protein binding of pharmaceuticals
696	Interaction of antibiotics with serum and its protein fractions
697	*In vitro* effect of sodium phenobarbital and diethylnicotinamide on the protein binding of bilirubin
698	Binding of oxytetracycline to serum proteins
699	Simulation of thyroid hormone-binding protein interactions in human plasma
700	Role of plasma protein binding in inhibitory effect of nortriptyline on neuronal uptake of norepinephrine
701	Reevaluation of thyroxine binding and free thyroxine in human serum; discussion of a new free thyroxine index
702	Drug-induced reduction of urate binding *in vivo* as related to effect of some uricosuric and anti-inflammatory drugs on binding of uric acid to human serum albumin *in vitro*
703	Effect of drugs on urate binding to plasma proteins
704	Flucloxacillin binding rate and capacity of binding to horse serum protein
705	Protein binding of psychoactive drugs with a tricyclic ring system in relation to their chemical constitution
706	Plasma protein binding of amphetamine, catechol, amines, and related compounds
707	Erythrocytes infected with chloroquine-sensitive *Plasmodium falciparum* binding chloroquine, with an apparent intrinsic association constant of 1.5×10^7 l./mole
708	Small changes in protein binding of drugs in plasma and tissues causing redistribution of highly bound drugs between tissues and plasma, resulting in concentration fluctuations of drug in plasma
709	Salicylate causing a release of long-chain fatty acids from their binding sites on human plasma proteins and bovine albumin
710	Review of protein binding of rifampicin
711	Interaction of warfarin and dicoumarol with human serum albumin
712	Effects of sulfonamides on protein binding of bilirubin

(670) concluded that the therapeutic differences in potency among four tricyclic antidepressant drugs known to inhibit the uptake of 5-hydroxytryptamine by human blood platelets depended more on their individual molecular structure than on the degree of binding to circulating proteins. In a similar study, data on the binding of imipramine, desipramine, and 3-chlorodesmethylimipramine to plasma proteins were obtained over a wide range of ligand concentrations, using a modified equilibrium dialysis technique. Plasma proteins other than albumin did not appreciably bind to the drugs studied, and the association constants of the complex were low. The authors concluded that apparently atypical binding behavior was disclosed for desipramine and 3-chlorodesmethylimipramine (671). The binding to bovine albumin of the model dyes and drugs bromcresol green, eosin, imipramine, and desipramine was studied, using an improved equilibrium dialysis technique. The dyes and drugs interacted with two to four types of binding sites through hydrogen bonding, electron donator–acceptor forces, van der Waals' forces, and hydrophobic forces. In addition, the drugs and dyes interacted with up to six binding sites through electrostatic forces. Desipramine binding exhibited a more complicated mechanism, probably involving exposure of additional binding sites upon a drug-induced conformational change (672).

The effect on diphenylhydantoin binding of some other drugs, including various antiepileptics, was investigated. Of these, only salicylic acid, sulfafurazole, and phenylbutazone (in clinical concentrations) decreased diphenylhydantoin binding. The clinical significance of this effect was discussed (673). The percentage of bound testosterone was significantly increased in hyperthyroidism and decreased in hypothyroidism. The *in vitro* testosterone saturation curves showed a remarkable increase in the testosterone-binding capacity of plasma in hyperthyroidism and a decrease in hypothyroidism. The study demonstrated that the state of thyroid function has a significant effect on the binding of testosterone and plasma, and it provides an explanation for the changes in the kinetics of testosterone metabolism observed in these disorders (674).

Additional references on the interaction of drugs with biological materials are provided in Table XIX.

Interactions of Drugs with Nonbiological Substances—A 1:2 complex between borax and chloramphenicol in aqueous solution was used to explain the relative stabilities of simple aqueous solutions of chloramphenicol (713). The molecular interactions in water of phenazine and tetramethylpyrimidopteridinetetrone with alkylxanthines and benzene derivatives were studied by means of the phase-solubility technique. These results were discussed in terms of structural similarity between interacting species. Studies concerning the effects of solvent on the extent of complex formation revealed that water plays a unique role in these interactions. The observation that complexation between two structurally dissimilar compounds is favored over that between two similar compounds suggested that some forces other than mere hydrophobic bonding should be considered. It was postulated

that the results are best rationalized by hydrophobic bonding stabilized by a type of bonding similar to polarization binding (714). On the basis of a simple model of 1:1 complex formation between planar molecules, the observation was made that there is no significant difference between the average behavior of neutral and charged complexes. The maximal overlap concept provides a general first-order description of molecular complex formation in aqueous solution. Application of the maximal overlap approach leads to average complex structures without introducing arbitrary assumptions about specific group interactions. The structures thus generated are consistent with the chemical reactivity of the complexes (715).

Maulding and Zoglio investigated the interaction of dihydroergotoxine with certain xanthines (716), dihydroergocrystine with xanthine analogs (717), and methysergide maleate and caffeine (718), and, in general, they discussed investigations into the nature of ergot alkaloid–xanthine complexes (719). These workers included solubility, dissolution, and partitioning studies to evaluate the *in vitro* interaction along with *in vivo* studies.

The quaternized vinylpyridine units of synthesized alkyl copolymers constituted the binding sites for *para*-toluene sulfonate ions. The stability of the complex formed in the reaction increased with an increase in temperature from 15 to 37° but decreased at 45°. The binding process was endothermic and associated with positive entropy effects, indicating that the polymeric model system described demonstrated properties expected for hydrophobic bonding. The effect of urea on the binding of sulfonate ion by one of the alkyl copolymers was studied and was found to be in keeping with the claim that urea breaks hydrophobic bonds (720).

Equilibrium and rate constants were calculated for the reversible covalent addition of bisulfite ion to 2-aminopyrimidinium ion and to its 1-methyl and 4-methyl derivatives. The 1:1 covalent adducts had very low solubility in aqueous buffers around pH 4. This was consistent with their being zwitterions. Rate-determining steps in adduct formation appeared to involve an attack of both the bisulfite ion and sulfite ion on the pyrimidinium cation. In the reverse reactions, the zwitterionic adducts appeared to decompose by both nonbase-catalyzed and specific base-catalyzed reactions (721).

Experimental data were obtained which appear to show that the binding between organic species dissolved in water apparently takes place most effectively between members of two large, distinct classes of structures, classified arbitrarily as A and B types. Many drugs may be included in the present classification; some examples for which data are available are: caffeine, theophylline, and prednisolone in class A, and phenacetin, promethazine, and menadione in class B. The complexing tendencies of series of systems involving pairs of interacting organic molecules in aqueous solution were investigated by the phase-solubility technique. Stability constants for some caffeine interactions were evaluated by means of partitioning studies (722). The effect of different organic solvents on the extent of complex formation in binary aqueous organic solvent mixtures was studied by various techniques. In every instance, the stability constant of the complexes decreased as the ratio of organic solvent to water increased. The complexes were much less stable in aqueous dioxane mixtures than in similar mixtures of water and polyhydroxy compounds, such as glycerin and sucrose. These studies strongly indicate the significant contribution made by hydrophobic bonding to these interactions and the major role of the water structure (723).

The interaction between bentonite and microcrystalline cellulose was studied in suspension and in the solid state. The rheological behavior of the mixed suspensions and the mechanical properties of composite films prepared by drying thin layers of these suspensions were investigated as a function of composition. Based on the volume percentage of the dry components, bentonite was about five times more effective in increasing the viscosity of aqueous suspensions than cellulose. Bentonite formed strong films when its aqueous suspensions were dried, while cellulose, either pure or in a mixture, did not (724). Interactions of isoniazid with magnesium oxide and with lactose were investigated in the solid state. In the isoniazid–magnesium oxide system, chemisorption, as well as physical adsorption, of isoniazid molecules onto the magnesium oxide surface was confirmed by diffuse reflectance spectroscopic data. The mechanism of surface chemisorption was noted to be different from that of the formation of the isoniazid–metal-ion complex in solution. The browning reaction of the isoniazid–lactose system in the solid state was also studied, and the reaction products confirmed the presence of isonicotinoyl hydrazones of lactose and hydroxymethylfurfural (725).

The interaction of ascorbic acid with silicic acid in the solid state was also studied using diffuse reflectance techniques. Adsorption of ascorbic acid from methanol solution by silicic acid did not occur; however, after evaporation of the methanol, ascorbic acid did undergo strong interaction with silicic acid, probably through hydrogen bonding. Thermal degradation of ascorbic acid in the adsorbed state was found to be different from that in solution. In acid solution, furfural was a major degradation product; in the adsorbed state, furfural could not be detected (726).

The kinetics of dialysis of a number of compounds in the absence of protein were studied in some detail to characterize the nature of the dialytic process and its dependency on experimental variables. It was shown that the rate of escape of a small molecule from a dialysis cell was a first-order process, provided that sink conditions were maintained (727).

Shima and coworkers studied the interaction of some pharmaceuticals with synthetic macromolecules. Their studies included the binding of pyrazolone and phenothiazine derivatives (728); barbituric acid, hydroxybenzoic acid, and xanthine derivatives (729); and other pharmaceutically important drugs (730) with styrene–maleic anhydride copolymer. The binding equilibria fitted a Langmuir-type equation, and molec-

Table XX—Additional References on Binding of Drugs to Nonbiological Substances

Reference	Topic
731	IR study of solute–solvent interactions of testosterone propionate
732	Determination of stability constants of hydroxyindoloquinoxaline metal complexes
733	Swelling of crosslinked polyacrylic acid by adsorption of water vapor
734	Gastrointestinal absorption of *O*-benzoylthiamine disulfide–polyacid complexes
735	Loss of ascorbic acid from tablets being directly proportional to the amount of water not bound by silica gel
736	Interaction of bishydroxycoumarin and furosemide with various adjuvants due to chemisorption proceeding by a mechanism similar to that of chelation
737	Solid–solid interactions of tetracycline, bishydroxycoumarin, and methantheline bromide significantly altering availability and activity of medicinal agents in pharmaceutical dosage forms
738	Effect of molecular interaction on permeation of organic molecules through dimethylpolysiloxane membrane
739	Riboflavin tetrabutyrate photodecomposed by methyl-substituted benzene derivatives through a 1:1 molar ratio complex
740	Inhibition of photodecomposition of riboflavin by 1:1 charge-transfer complexes of pyrazolone derivatives
741	Presence of polyacrilin potassium in formulation not affecting total drug availability in gastrointestinal tract
742	Divalent metals complex with 5- and/or 6-alkyl-substituted thiouracils
743	Interaction between sodium dehydroacetate and flavins
744	Effect of added salt on interaction between polymer and detergent in aqueous solution
745	Depreciating interaction of disinfectants and preservatives with nonionic surfactants
746	Effect of a polymeric complexing agent on liberation and stability of chloramphenicol
747	Interaction of polysorbate 80 (Tween 80) and polyvinylpyrrolidone with papaverine HCl
748	Interaction of sodium dodecyl sulfate with methylcellulose and polyvinyl alcohol, showing the existence of a critical concentration of sodium dodecyl sulfate below which no interaction with the polymers occurs
749	NMR investigation of sodium-ion binding in solutions of sodium caprylate and water in caprylic acid
750	Tryptazine reacted with methyl orange at pH 3.5 to form a 1:1 color complex
751	Silicone rubber and polyvinyl chloride strongly bind lipophilic drugs, while hard plastics like Teflon do not
752	Investigation of interaction between metal ions and alkyl phosphate monolayers at air–water interface
753	Solution confirmation of valinomycin–potassium-ion complex
754	Hexachlorophene esters in pure and mixed monomolecular films interacting with fatty acids, fatty acid alcohols, and fatty acid esters
755	Interaction of macromolecular and surfactant excipients with insoluble drugs used in pharmaceutical suspensions
756	Temperature dependence of the formation constants of alkaloid–methyl orange complexes
757	Stability of dispersed systems as affected by specific chemical interaction
758	Metal complexes of selenocysteamine
759	Stability constants for some 1:1 metal–carboxylate complexes, showing stabilities of complexes to be directly related to basicities of anions
760	Preassociation and thermodynamics of hydrophobic hydration in dilute solutions of surfactants
761	Kinetics of copper (II)–ethylenediamine complex formation
762	Interaction of nonionic macromolecular agents with methylhydroxybenzoate, indicating preservative activity due to permeability of microbial membrane
763	Chromatographic evidence for interaction of certain drugs with nonionic macromolecular agents
764	Counterion binding in micellar solutions of 1-*n*-dodecylpyridinium iodide
765	Aspirin interacting with paracetamol in tablets to produce increased amounts of alicyclic acid and diacetyl-*p*-aminophenol
766	Interaction between reserpine and desmethylimipramine
767	Effect of procaine hydrochloride concentration on formation of insoluble complex with sodium lauryl sulfate
768	Interaction between procaine or tetracaine and thiamine, showing evidence of charge-transfer complex
769	Effect of varying concentrations of testosterone on CMC value of lauryltrimethylammonium bromide, noting possible effect of steroid on enthalpy and entropy of micellization and micellar structure
770	Pharmacological aspects of rauwolfia–reserpine complex
771	Effect on Donnan equilibrium, neutral salts, and varying pH on degree of binding of some drugs to macromolecules, showing degree of binding increased when direction was from uncharged to negatively charged drug molecules

ular orientation and structure were used to explain the magnitude of binding.

Additional studies involving the interaction of drugs with nonbiological substances are found in Table XX.

Surface Phenomena—The various publications dealing with surface phenomena have been subdivided to aid the reader in locating areas of specific interest. Because of the obvious overlap in this subject matter, the reader who needs a thorough review is advised to consider the entire section.

Interface Studies—Cellulose acetate butyrate, cellulose acetate stearate, and cellulose acetate phthalate were studied as monolayers at the air–water interface. Monolayers of the first two compounds were virtually unaffected by changes in subphase pH, whereas cellulose acetate phthalate exhibited large differences under the same conditions. Certain monolayer properties of the cellulose esters were used to interpret the behavior of these polymers as free films and as enteric coatings (772). At pH values of 2–4, cellulose acetate phthalate monolayers were uncharged and were arranged in a compact, coherent form. An increase in pH brought about partial ionization and marked changes in monolayer organization. The effects of charge repulsion and increased solvation of charged groups caused marked expansion and decreased the stability of cellulose acetate phthalate monolayers. The greatest effect of pH on monolayer properties appeared to occur in the vicinity of pH 6 (773).

Using the Haydon–Taylor model, in which the surfactant head groups are situated at some distance from the oil surface, the interaction energy of electrostatic repulsion between oil droplets and dilute electrolyte solutions was derived for the two cases: constant-surface potential and constant-surface charge. For comparison, the repulsive energy was also derived for the constant-surface charge case without the effect of this adsorbed layer model. The model accounted for the penetrability of the electrolyte and dielectric constant in the adsorbed surfactant layer of varying thickness, the degree of surface coverage, particle-size effect, ionic strength, and the dielectric constant in the bulk solution. In the constant-potential case, the resulting

equation is identical to the classical DLVO one. Computations showed that as flat plates and spheres approached each other, constant-surface charge with impenetrable adsorbed layer was > constant-surface charge with penetrable adsorbed layer > constant-surface potential. It was noted that because of the possible 50- to 100-fold difference in magnitude between them, the choice of the proper model is important when one considers applying the theory to the rigorous kinetic treatment of the coalescence of o/w emulsions and flocculation of suspensions (774).

The adsorption from solution onto griseofulvin powder of a series of nonionic detergents of the polyoxyethylene glycol monoalkyl ether type was described. Results were also given for polyethylene glycol 400 and a new detergent, pentaerythritol mono-*n*-octyl ether, whose synthesis and purification were reported. The effect of temperature on the adsorption was studied, and possible explanations for variations in adsorption with temperature were based on the orientation of the molecules at the interface; this was deduced from measured molecular areas (775).

The kinetics of transfer of cholesterol from an aqueous polysorbate 80 solution into hexadecane and vice versa were studied by means of the multiparticulate dispersion technique. The experimental data were quantitatively analyzed by the physical model which accounts for the effects of bulk diffusion, interfacial resistance, interfacial area, and the lipid–water partition coefficient. For the 0.1% polysorbate 80, a P value of around 1.7 to 2.2 $\times$ 10^{-7} cm. sec.$^{-1}$ was found that was consistent with all data on water-to-oil as well as oil-to-water transfer experiments. These findings suggest that such large nonspecific interfacial barriers are important in many biological and biopharmaceutical situations (776).

Ghanem *et al.* (777) investigated the effects of an interfacial barrier in interphase transport. These procedures were applied to the study of the effects of an adsorbed gelatin at the hexadecane–water interface upon the transport of diethylphthalate between the two phases. By employing diethylphthalate as the solute, the transport data were analyzed by a physical model. The two ionic surfactants, sodium lauryl sulfate and dodecylpyridinium chloride, markedly decreased the interfacial barrier, even at low concentration. The analysis also showed that neither the electrolyte type nor concentration influenced the permeability coefficients, although they significantly altered the interface transport rates themselves by changing the partition coefficients. These findings may represent types of nonspecific situations that give rise to important barriers in *in vivo* drug transport. Ghanem and coworkers studied the quantitative transport behavior of several organic solutes in matrix systems composed of micron-size hexadecane droplets dispersed in an aqueous gelatin gel in which the oil–water interfacial barrier to transport was expected to play an important role. The authors stated that the techniques developed in the investigation should be useful in the quantitation of interfacial barriers in the oil–water interface transport of solutes and in the separation of various bulk diffusional resistances from interfacial resistances in complex multiphase matrixes (778).

Table XXI—Additional References on Interface Phenomena

Reference	Topic
779	Interaction of nitrogen dioxide with cholesterol monomolecular films and the possible biological relevance
780	Peculiarities of adsorption films of macromolecules and their relation to stability of emulsions, showing their tendency to form two-dimensional networks within long periods
781	Behavior of surface-active agents and dyes at oil–water interfaces, showing influence of binding between dye and surface-active agents as influenced by the species and concentration of electrolyte in aqueous phase
782	Isoelectric points of phospholipids at oil–water interface
783	Thickness and physical properties of interfacial films stabilizing emulsions formed at oil–water interface
784	Relative adsorbability of counterions at charged interface
785	Review of solid–liquid interfaces
786	Interfacial pressures and viscoelasticity measurements of monolayers of bovine serum albumin and its derivatives, showing effect of chemic l structure of bovine serum albumin
787	Surface pressure and specific water-evaporation resistance of monolayers of aluminum stearates, demonstrating effects of intermolecular interaction
788	Review of recent developments in interfacial phenomena
789	Estimation of film thickness from cohesive pressure at air–water interface
790	Review of fundamentals of monomolecu ar films including their importan :e in biological processes

Additional references on interface studies are described in Table XXI.

Adsorption Studies—In an approach to understanding the membrane action of phenothiazines, the adsorption from solution was investigated, using such adsorbents as carbon black, graphite, silica gel, and polyethylene. The results were related to other physicochemical properties and biological activities of the drugs. The adsorbed amount was influenced by the molecular volume of R_{10}'N at the 9-position, the sulfoxide group at the 5-position, and the bulkiness of the substituent at the 2-position. The adsorbed amount increased with the pH of the buffer solution between 5 and 8, and it was considered that pH had an influence on the hydrophobic and hydrophilic balance of the molecule. The decrease in adsorption with addition of urea demonstrated that the adsorption of phenothiazines proceeded on the hydrophobic interaction (791). The adsorption of sulfonamides by carbon black from solution was considered to be a hydrophobic interaction, noting that the entropy change was positive (792). The introduction of a methyl or methoxy group into the sulfonamide molecule caused an increase in the adsorption of the sulfonamide by carbon black, an increase in the binding to bovine serum albumin, and an increase in the absorption of the sulfonamide from the rat small intestine. It was concluded that hydrophobic interaction between the various sulfonamides and the intestinal membrane formed an important factor in absorption phenomena (793).

Methylene blue was adsorbed by potato starch from aqueous solution as a monomer or dimer, depending upon its concentration. Water-miscible additives such as methanol, dioxane, sucrose, and urea shifted the monomer–dimer equilibrium of the dye in the direction

Table XXII—Additional References on Adsorption Phenomena

Reference	Topic
799	Surface chemical properties of disodium and dipotassium monoacetyl phosphates; differences in these properties being attributed to the lower water solubility of the sodium salt, resulting in easier adsorption and micelle formation
800	Influence of thixotropic agents (Aerosil and Aerosil R 972) on adsorption of water by powders
801	Effect of hydrocarbon chain length on adsorption of sulfonates at solid–water interface
802	Influence of pH on adsorption of aromatic acids on activated carbon, showing marked increase in adsorption from aqueous solutions at pH's below 7
803	Adsorption of starch and oleate and interaction between them on calcite in aqueous solutions
804	Differential heats and entropies of water adsorption on calcium and potassium montmorillonite
805	Review of adsorption of cationic surfactants by cellulosic substances
806	Adsorptive property of aluminum hydroxide for vaccine being reduced, depending on method of preparation of adsorbed vaccine, superficial structure, and crystalline form of aluminum hydroxide
807	Phase relations involving deposition of cholesterol from triglyceride solution, noting the hydrogen bonding of cholesterol to the ester bond of the triglyceride being unrelated to solubility of cholesterol in the triglyceride
808	Removal of long-chain, nonionic ethylene oxide adducts from aqueous solutions by adsorption
809	Adsorption of sodium alkyl sulfates at air–water interface, showing various stages of forces acting at interface
810	Review of theoretical approaches applied to studies of adsorption from concentrated and diluted binary mixtures
811	Adsorption of *s*-triazines by montmorillonite as a function of pH and molecular structure, showing that more basic compounds were adsorbed in greater amounts
812	Adsorption of aerosol OT at solid–liquid interface
813	Adsorption of ionized surface-active agents in solution at air–solution interface
814	Amylose–iodine–iodide complex as a model for competitive cooperative linear adsorption
815	Adsorption of bovine serum albumin at air–water interface shown to be reversible; measurement of equilibrium adsorption isotherm
816	Adsorption of ionic surface-active agents influencing stability of hydrophobic colloidal dispersions
817	Measurement of the amount of sorption water in various kinds of starch samples in equilibrium with water at 25 and 40°
818	Kinetics of adsorption from solution in which rate expression yields rate constant for adsorption and desorption simultaneously
819	Effect on adsorption of increasing the number of methyl groups in an homologous series of surface-active agents such as alcohols and alkanoic acids
820	Adsorption of polyvinyl alcohol on titanium dioxide
821	Influence of sodium dodecyl sulfate on the stability of iron (III) hydroxide and aluminum hydroxide sols
822	Adsorption of anionic surfactants on montmorillonite, as proven by X-ray diffraction data
823	Simple model for calculating heat curves for physical adsorption
824	Adsorption of dyes and their surface spectra
825	Review of mathematically treatable quasithermodynamic and statistical models in adsorption from solution
826	Review of adsorption of cationic surfactants on various solid substrates, including certain biological substances
827	Model for the adsorption of weak electrolytes on solids as a function of pH, using carboxylic acid–charcoal system
828	Adsorption equilibrium of ionic surfactants in the presence of an inorganic salt in solution
829	Adsorption of surfactant molecules at a liquid–vapor interface; variation in rates of adsorption and adsorption energies with increasing concentration of the surfactant solutions discussed in terms of detergent effectiveness of surfactant
830	Alumina surface chemical properties determined with colored indicators
831	Review of importance of physical adsorption and the information that it can provide regarding nature of a solid surface

of the monomer and reduced the extent of methylene blue adsorption without significantly affecting the maximum possible adsorption, indicating that additives act primarily on the effective concentration of the dye (794). In studying the effects of the adsorption of benzoic acid on graphite, it was concluded that the adsorbed acids were mostly oriented flat on the graphite surface; plane-to-plane stacking between the acid molecule and the fused benzene ring plane of graphite seemed to be dominant among the possible adsorption forces (795). The velocity and activation energies for adsorption and desorption of cyanocobalamin on talc from aqueous solutions were investigated. The activation energies for the adsorption and desorption were 1.16 and 3.98 kcal. $mole^{-1}$, respectively, using the Arrhenius equation. It was indicated that cyanocobalamin is energetically more stable in the adsorbed state than it is free in solution, because the activated states for the adsorption and the desorption were considered to be identical (796).

Intravascular thrombosis was shown to be an interfacial reaction dependent on the surface charge characteristics of the blood vessel wall, blood cells, and prosthetic materials. Positively charged prosthetic materials were thrombogenic, whereas negatively charged surfaces tended to be nonthrombogenic; the higher and the more uniform the negative charge density, the better was the chance of the materials being nonthrombogenic (797). An investigation of the interactions of the cholesterol particle surface with bile salts and alkyl surfactants was undertaken. Microelectrophoretic and adsorption techniques were used to demonstrate, in contrast to the alkyl surfactants, that the adsorption of bile salts on the cholesterol particle surfaces was much less than expected in the concentration ranges studied. While these results are initially surprising, the data are consistent with the idea that the relatively rigid bile salt molecules can adsorb only onto specific sites on the cholesterol surfaces, while the more flexible alkyl surfactants can more readily interact (798).

Additional references on adsorption studies are provided in Table XXII.

Studies on General Properties of Surface-Active Agents—The effects of pH and hexachlorophene on the net fixed-charge density of the colloids composing the epidermal surface were studied *in vivo*, employing human subjects. The results were shown to be analogous to titration curves of amphoteric macromolecules. Both the control and hexachlorophene titration curves were nonhysteretic when initiated at either extreme of the pH range, indicating reversibility of the observed pH and hexachlorophene-induced changes. The presence of hexachlorophene decreased the net fixed-

charge density of the tissue surface below pH 5.6; above this pH, a net increase was constantly observed. It was hypothesized that hexachlorophene-induced alterations in fixed-charge density result from allosterically effected changes in the dissociation constants of ionogenic protein side groups located vicinally to hexachlorophene interaction sites (832).

To elucidate the interaction of surfactants with biological membranes, the composition of epidermal phospholipids and the rate of biosynthesis of major phospholipid components were determined, using various analytical techniques. The major lipid components were cholesterol, lecithin, lysolecithin, phosphatidyl ethanolamine, and sphingomyelin. The biosynthetic and turnover rates of all identified phospholipids were greatly increased in the surfactant-treated skin. It was suggested that the tested surfactants damaged the epidermal membranes. A role of surfactants in increasing the absorption of medical substances was also proposed, in view of these results and other reports regarding the effect of surfactants on biological membranes (833). Shinoda (834) stated that, unlike ordinary solutions, an aqueous solution of nonionic surfactant resembles, in principle, a fine dispersion of two phases. One is the water phase, containing a very small amount of nonionic surfactant, and the other is the swollen surfactant phase. The thermodynamic properties, as well as the mechanism of dissolution, of biopolymers and polysoaps can be explained by the proposed model.

Although an HLB value is assigned to a definite surfactant, the real HLB of the surfactant at the oil–water interface changes with the amount and kinds of added salts in water as well as with the types of oils. On the other hand, the phase-inversion temperature of emulsions accurately reflects that the real HLB of a surfactant in a given system changes sensitively with the amount and kinds of added salts. It was found that the phase-inversion temperature of the emulsions studied was depressed about 14° in the presence of 6% sodium chloride solution, indicating that the HLB value of the surfactant was depressed about 0.8–1.0 unit in the solution (835). Solubility parameters were calculated for a homologous series of alkyl polyglycol monoethers with a variable glycol chain. These parameters were compared with the HLB values for the same surfactants. By considering the contribution made to the overall solubility parameter of a surfactant molecule by the solubility parameter of the hydrophobic portion of the molecule, a practical relationship between solubility and HLB was obtained. This relationship was valid, irrespective of the size of the hydrophobic or hydrophilic group, for compounds containing up to 20 carbon atoms or 20 ethylene oxide units in the alkyl or glycol chain, respectively. By making several assumptions, it was shown that heats of hydration and CMC's of surfactant, which have been shown to be related to HLB values, may also be related to solubility parameters of surfactant molecules (836). In studying the importance of surfactant location and required HLB in emulsification, Lin (837) noted that, for an o/w emulsion, placing the surfactants in the oil phase produced more stable emulsions than the same system prepared by initially placing the surfactants in the aqueous phase.

Table XXIII—Additional References on General Properties of Surface-Active Agents

Reference	Topic
838	Mutual relations among properties of cationic surfactants, such as solubility, micelle formation, and solubilization of water in nonpolar solvents, explained by hydration and difference in the ionic character of polar groups in surfactant molecules
839	Effect of ionic head of cationic surface-active agents on their hemolytic activity, showing that the number of carbon atoms in the alkyl radical, when less than 8, is related to hemolytic activity of cationic agent
840	Nonmicellar association of surfactant ions, noting constant enthalpy of dimerization for each chain length
841	Structure of aqueous surfactant solutions
842	New amphoteric surfactant having ether bonds in the molecule
843	Review of ethoxy sulfate-type surfactants and their colloid-chemical properties
844	Review of chemistry and technology of surfactants
845	Effects of temperature and hydrophilic chain length of nonionic surfactants on emulsion properties discussed in connection with the phase-inversion temperature of respective systems
846	Electrolyte flocculation of macromolecular stabilized emulsion in the framework of DLVO theory, with special reference to sodium alginate and gum arabic as emulsifiers
847	Review of esters of pentaerythritol and higher fatty acids, as well as their polyoxyethylene derivatives as surfactants
848	Application of nonionic surface-active agents for dispersion of pigments in aqueous media, noting that each surfactant had an optimal HLB value at which dispersion was maximum
849	Incipient flocculation properties of aqueous polymer dispersion which are stabilized solely by polyethylene oxide moieties
850	Dependency of detergency on HLB of nonionic surfactants being small for hydrophilic fabrics but large for oleophilic fabrics
851	Surfactant-ion activity of magnesium dodecyl sulfate in aqueous solution
852	Mechanism of action of a surface-active stabilizer of clay suspensions; stability of the suspension being adequate in the presence of up to 10–15% of electrolyte; at higher concentrations, addition of 1–1.5% algin being required
853	Review of classification of surfactants by HLB system
854	Review of ampholytes, their properties, and applications
855	Preparation and properties of sodium sulfoalkyl alkanoates surfactants
856	Langmuir film balance and surface-tension measurements for determining HLB of surface-active agents
857	Review of surfactant structure and performance
858	Review of application of surfactants in pharmaceuticals, including a table of toxicity of surfactants
859	Review of properties and uses in cosmetics of amphoteric surfactant cycloimidium
860	Review of effects of surface-active agents on absorption, solubility, and therapeutic utility of various drugs, including bacteriostatic agents
861	Surface properties of cellulose acetate phthalate, including claim that there is no evidence of stoichiometric complex formation with plasticizers, and interaction appearing to be completely nonspecific

Additional studies on general properties of surface-active agents are provided in Table XXIII.

Micelle Studies—The effect of change in pH on the CMC of a nonionic surfactant (polysorbate 80) was investigated; a linear relationship existed between the free energy of micellization and pH. The significance of changes in the enthalpy and entropy of micellization was discussed; both micellar molecular weight and the hydration per unit mass of surfactant decreased with an increase in pH value (862). The thermodynamics of

Table XXIV—Additional References on Micelles

Reference	Topic
868	NMR studies on micelle formation by promethazine hydrochloride
869	Properties of aqueous solutions of surface-active agents when their concentrations are below the CMC
870	Fluorescence and differential UV studies of micellar solutions of sodium phenylundecanoate
871	Biradical spin-labeled urea derivative used for studying the dynamic structure of sodium dodecyl sulfate micelles, showing the biradicals form aggregates in the micelles when present in excess in solution
872	Phospholipid bilayer–micelle transformation
873	Shift of NMR signal caused by micelle formation
874	Review of salt effects on CMC's of nonionic surfactants
875	Thermodynamics of micellar equilibrium for ionic detergents
876	Effect of change of solvent on CMC of a nonionic surfactant
877	CMC of Manoxol OT and Nonidet P40, using silver-110m as a tracer
878	Micelle size of barium dionyl naphthalene sulfonate in low polarity solvents by vapor-pressure osmometry
879	Counterion binding to reversed micelles by nuclear magnetic quadrupole relaxation of bromine-81
880	Interaction of acidic dye molecule with positive charges on micelle surface
881	Surface-active properties of ammonium salts of sulfated esters of oleic acid
882	Aggregation of local anesthetics in solution, demonstrating that hydrophobic substitution on the tetracaine *para*-amino group accounted for greater tendency to aggregate
883	Effect of temperature on micellar properties of pure nonionic surfactants; thermodynamic calculations
884	Effect of position of ester group on CMC of ester-linked sulfonates, showing that for a given number of carbon atoms in the alkyl chain, the log CMC value increases regularly with a change in the ester group away from the terminal position to more central positions in the hydrocarbon chain
885	Solubility and CMC's of fluorinated surfactants in water
886	Ultrasonic absorption in aqueous solutions of ionic amphiphiles, with interpretation of results from weakly concentrated micelle solutions
887	Salt effects on the CMC's of nonionic amphiphiles
888	Kinetics of micelle dissociation by a light-scattering temperature jump method
889	Prediction of the CMC of mixtures of alkyltrimethylammonium salts using Shinoda's equation for CMC of a multicomponent soap mixture
890	Thermodynamics of micellization and micellar molecular weights of zwitterionic *N*-alkyl betaines by light scattering and vapor-pressure osmometry
891	Potentiometric and calorimetric studies of the structure of some soap solutions with short paraffin chains
892	Influence of charge on the micelle size of a zwitterionic surface-active agent
893	Statistical treatment of micellar solutions
894	Effect of temperature and solubilization of hydrocarbons on mean micellar weights in aqueous sodium oleate solutions
895	Effects of counterion and temperature on micellar properties of dihydroxy and trihydroxy bile salts
896	Effect of temperature on CMC of tetradecylpyridinium bromide, tetradecylbenzyldimethylammonium bromide, and tetradecyltrimethylammonium bromide

micellization of three nonionic surfactants in mixed solvents were reported. The contribution of the alkyl chains of the surfactant molecules to micellization was estimated from solubility data (863). The optical rotatory dispersion of a nonionic surfactant, β-D-octyl glucoside, was investigated in aqueous solutions in the UV region. The specific rotation at any wavelength showed an increase at the CMC, which could be determined reliably from the change in specific rotation. The rotatory dispersion curve for the surfactant in micellized form was derived and compared with that of the nonmicellized surfactant below the CMC. The change was small and was ascribed to a "medium" effect, arising from the difference in the local refractive index at the micelle surface as compared with the bulk solvent. This interpretation is compatible with currently accepted ideas on the fluid nature of the micelle core, and it suggests a lack of any conformational restraint at the micellar interface (864). The temperature dependence of the CMC of decyl-, dodecyl-, and tetradecyl-α-picolinium bromides was determined by measuring conductance. Constants for the equation relating log CMC and alkyl chain length were calculated for the temperature range 5–70°. An estimate of the effect of temperature upon the degree of counterion binding was recorded. Thermodynamic parameters were calculated using the uncharged phase-separation model, and a theoretical interpretation of the process of micellization was given (865).

The weight-average aggregation numbers and micellar molecular weights for homologous zwitterionic *N*-alkyl betaines were determined by light scattering. A linear relationship was found between the logarithm of the weight-average aggregation number and the alkyl chain length for C_{10}, C_{11}, C_{13}, and C_{15} homologs. As the temperature was raised, a trend was observed in that the weight-average aggregation numbers and the micellar molecular weights for the homologs increased, reached a maximum, and then decreased. This behavior was related to changes in the CMC with temperature (866). The acid dissociation constants of long-chain esters of carnitine above the CMC were determined potentiometrically at several concentrations of added KCl. As the degree of protonation increased, the apparent pK values decreased, owing to the increased positive charge on the micelle. The difference in pK between the neutral (zwitterionic) micelle and the value at any given protonation was used to determine the surface potential of the micelle at that degree of protonation. From the partial molal volume of each surfactant in the micelle and the calculated surface charge density, it was possible to calculate the aggregation number of the micelle. Good agreement was noted between the calculated values of the micelle and the values obtained from light-scattering experiments at several ionic strengths and degrees of protonation (867).

Table XXIV provides additional references on micelle studies.

Additional studies of a general nature involving surface phenomena are provided in Table XXV.

Crystallization—The results of crystal growth-rate studies, using single crystals of sulfathiazole and methylprednisolone, were presented. The growth rate of sulfathiazole crystals growing in a supersaturated aqueous solution showed stirring rate dependence from 10 to 400 r.p.m. for all three faces studied. In alcohol solutions, the stirring rate dependence appeared to disappear above 150 r.p.m., suggesting that at the higher stirring rates the rate of crystal growth of sulfathiazole was surface controlled. A plot of the growth-rate *versus* the supersaturation ratio appeared to be linear for all studies, with intercepts exhibited on the supersaturation ratio axis. The intercept appeared

Table XXV—Additional References on Surface Phenomena

Reference	Topic
	General Studies on Colloids, Gels, and Sols
897	Interaction of two identical spherical colloidal particles at great distances, using the Derjaquin equation
898	Electric conductivity of gels of natural macromolecular substances, showing that three types of water structure exist in various gels
899	Review of properties of association colloids, isolated thin film, surface forces, and disperse systems
900	Review of stability and flocculation of typical lyophobic and lyophilic colloids, solutions containing simple ions, and nonionic surface-active agents
901	Adsorption of water vapor by gelatins being independent of molecular weight of the gelatin but dependent on ionization state of free carboxyl groups
902	Pulsed NMR study of temperature hysteresis in agar–water system, indicating that the major portion of water molecules in this system is not in an "icelike" or modified state
903	Review of methods for determining force of adhesion between colloidal particles and factors that influence adhesion between a sphere and a plane and between a plate and a plane
	Foam Studies
904	Foaming characteristics of anionic surfactants, volume of foam increasing with concentration of surfactant up to a certain value and then leveling
905	Action of electrolytes on foam stability of a nonionic surface-active agent, showing the increasing stability as a function of the concentration, as it relates to the surface tension and the CMC
906	Surface hydrolysis enhancing the inevitable pH changes in foam separation of anionic surfactants
907	Effects of surface-active agents on bubble formation
	Surface Area Studies
908	Orientation of monolayers of half-esters of polymethylvinyl ether maleic anhydride, showing effects of subphase pH and certain water-soluble plasticizers on surface pressure–area isotherms
909	Proposed methods for surface area determination based on behavior of adsorption isotherms of completely miscible liquid pairs
	Wetting and Contact Angle Studies
910	Effect of ionic-type surfactant pretreatment in contact angle studies on viable human skin
911	Adsorption and wetting phenomena associated with Graphon in aqueous surfactant solutions
912	Wettability of chloramphenicol palmitate, demonstrating lack of apparent relation between HLB values and wetting efficiency
913	Spreading coefficients, wetting energies, and adsorption of surfactants
914	Review of wetting phenomena of solid surfaces
	Surface-Tension Studies
915	Effect on surface activity of some phenothiazine derivatives due to changes in number of alkyl groups, degree of branching, and number of dissociable groups on alkylamino portion of the molecule
916	Surface activity of water–1,4-dioxane system
917	Electric surface potentials and surface tension of organic bases in aqueous solutions
918	Dynamic surface tensions of surfactants in natural hard waters
919	Comparative studies on interfacial tension of different ointment bases with water–oil emulsifiers
920	Surface activity of aqueous solutions of chlorohydrins depending mainly on the weight ratio of hydrophilic to hydrophobic groups
	Diffuse (Electrical) Double-Layer Studies
921	Approximate methods of determining double-layer free energy of interaction between two charged colloidal spheres
922	Review of Helmholtz free energy for electrochemical double layers of charged colloidal particles in aqueous medium
923	Interfacial instability due to electrical forces in double layers—general considerations
924	Interfacial instability due to electrical forces in double layers—stability of interfaces with diffuse layers
925	Electrical double layer at the graphite–surfactant interface

to be a function of its solvent, varying from 1.07 to 1.43, and to be a function of the polarity of the alcohol. The crystal growth rate of methylprednisolone, on the other hand, showed no stirring rate dependence in the range from 20 to 400 r.p.m. and appeared to be surface controlled even at low stirring rates (926).

The results of polyvinylpyrrolidone inhibition of sulfathiazole single-crystal growth were reported. The minimum concentration of polyvinylpyrrolidone required to inhibit crystal growth completely was a linear function of the supersaturation ratio, with an intercept of approximately 1.15 exhibited on the latter axis. The minimum concentration of polyvinylpyrrolidone required for complete inhibition of crystal growth was a function of the molecular weight of polyvinylpyrrolidone. The results of using polyvinylpyrrolidone molecular weights of 10,000, 40,000, and 360,000 are presented. The data suggest that the inhibition point depends on the relative rates of transport of polyvinylpyrrolidone and sulfathiazole to the crystal surface from the bulk of the solution. A model is presented that appears consistent with the data (927).

The crystal structure of the 2:1 complex of barbital with caffeine was determined by X-ray diffraction methods. The block-diagonal least-squares refinement of 496 atomic positional and thermal parameters, based on 4665 X-ray intensity data, gave a final R factor of 0.05. The structure consisted of ribbons of barbital molecules linked by NH---O=C hydrogen bonds. Caffeine molecules were bound to the ribbon by an NH---N(9) hydrogen bond and by an unusual interaction involving C(8)H with two barbital oxygen atoms. Weak interactions of nonhydrogen-bonded caffeine carbonyl groups with barbital carbonyl groups may also be important in this crystal. There was minimal overlap of the flat ring systems of the component molecules (928).

Additional references on crystallization are found in Table XXVI.

Rheology—A chemical balance provided a simple, cheap, and readily available method of assessing the consistency of biological fluids such as sputum. A scale reading at an arbitrary time provided a useful empirical parameter which could be employed in routine testing of chemical samples and in the assessment of mucolytic agents. This reading also correlated well with data obtained using a conventional cone and plate viscometer. The change of scale reading with time could be analyzed in a fundamental rheological manner, using the linear viscoelastic model. The method of measure-

Table XXVI—Additional References on Crystallization

Reference	Topic
929	Macroscopic appearance of frozen and dried samples in connection with growth of eutectic crystals; an optimum temperature range to promote the eutectic crystallization for each solute
930	Change in the macroscopic appearance during freezing, and the critical temperature necessary for freeze drying of pharmaceuticals
931	Review of recent theories of growth and dissolution of crystals, their importance in biological and physical systems, and the role of foreign substances as inhibitors of these processes

ment was nondestructive and allowed repeated measurements to be made on the same sample (932).

The rheology of six grades of white soft paraffin was investigated, using continuous shear viscometry and a creep viscometer. Working the samples on a triple roller mill decreased the apparent viscosity and, initially, increased the yield stress. Five of the grades were linear viscoelastic and one was nonlinear viscoelastic. The nature of ductility and its relation to measured rheological parameters were discussed (933). The viscoelastic gel in the continuous phase of a liquid paraffin–water emulsion stabilized by a mixed emulsifier of cetrimide and cetostearyl alcohol was similar to that formed by dispersing cetrimide and cetostearyl alcohol in water. The effects of temperature changes on the rheological properties of the emulsion and the ternary system were examined in continuous shear and in creep, and variations in the viscosities and compliances were correlated with the thermal phase transitions determined microscopically. The emulsion and the ternary systems were of maximum consistency at approximately 38 and 43°, respectively. These temperatures represent the transition from the frozen smectic to the liquid crystalline phase. At higher temperatures, the compliances rose and the viscosities fell as the network weakened and finally dissolved to form an isotropic solution (934).

Additional studies on rheology are provided in Table XXVII.

PHARMACEUTICAL ASPECTS: ANTIBIOTICS

Some studies of the oral absorption of dicloxacillin from various pharmaceutical formulations in beagle dogs suggest that the female of this species shows consistently higher and more prolonged blood serum levels of the antibiotic than the male. These studies suggest that there are variations in the level of monobasic penicillin molecules in blood serum after oral administration that are related to the sex of the animal, while a similar correlation does not appear to exist for the amphoteric penicillins. Determination of the biological half-life of the various penicillins in the male and female after intravenous administration indicated that there was no difference in the sexes with respect to the disappearance of active drug from the blood (956).

The absorption of tetracycline from the rat stomach was investigated at acid pH values. The absorption was dependent upon the anion and the surface activity of the buffer (957).

Spectinomycin slowly inhibited the steady-state growth of *E. coli* to a new steady state with a new rate constant that was linearly dependent, above a certain minimum, on the concentration of spectinomycin. This minimum concentration is a function of the concentration of the media and can be assigned to binding or removal of microbiologically effective spectinomycin as protonated material by the components of the media. The logarithm of the inhibitory constant increases linearly with the pH of the media to pH 7.6, which implies that only uncharged material is biologically active. The slow rate of achievement of a drug-equilibrated, steady-state, microbial generation rate can be reconciled with a relatively rapid reequilibrated rate on dilution with fresh media by postulating depletion of a cell-generated vital metabolite linked to the growth rate of microorganism (958).

The closely related antibiotics diumycin A and B, with monomeric molecular weights of approximately 1800 daltons in ethanol, aggregate in aqueous buffers to form particles with a molecular weight of at least 32,000 daltons. The aggregate of diumycin was essentially unaffected by esterification of the acid, acetylation

Table XXVII—Additional References on Rheology

Reference	Topic
935	Rheological measurements of semisolids, including evaluation of relationship between shear stress and shear rate, determination of product behavior during continuous shear, and characterization of static structure of the product
936	Shear-dependent interaction of plasma protein with erythrocytes in blood
937	Review of inorganic thickening, suspending, and emulsion-stabilizing agents
938	Use of rheology in pharmaceutical technology
939	Measurement of properties of semisolids, with emphasis on viscoelasticity, continuous shear, creep, and oscillation
940	Changes in rheological properties of vaselines connected with their content of cycloparaffinic and low paraffinic fraction
941	Viscosity of oxyethylated alcohols of wool fat
942	Rheological properties and composition of petrolatums
943	Importance of rheological parameters of bases for ointments in determining rate of liberation and sorption of drugs incorporated in them
944	Effect of pharmaceutical additives on rheological characteristics of dispersions of methylhydroxyethylcellulose
945	General flow characteristics in rheological evaluation of dispersions of methylhydroxyethylcellulose
946	Rheology of clay mineral suspensions
947	Review of rheology of disperse systems, dealing mainly with pigments and paints
948	Influence of particle-size distribution on apparent viscosity of non-Newtonian dispersed systems
949	Effect of glyceride distribution on rheological properties of fats
950	pH dependence of rheological properties of agar–agar hydrogels
951	Rheological properties of alginic acid gels
952	Rheological properties of hydrogels of agar–agar and stress relaxation of concentrated agarose gels
953	Rheological properties of concentrated pectin gels made through diffusion of alcohol at room temperature in concentrated subacid pectin solution
954	Review of mixing of Newtonian and non-Newtonian fluids
955	Influence of production scale-up upon quality of a cream, including changes occurring in hardness, particle-size distribution, and rheological properties

of hydroxyl groups, high ionic strength buffer, or variations in pH from 2.2 to 12.4. These results indicate that salt linkages and hydrogen bonds contribute only slightly to stabilize the aggregate. The aggregate may be disrupted by: (*a*) the addition of such hydrophobic bond-breaking agents as buffered aqueous solutions of guanidinium chloride, urea, or formamide; (*b*) the hydrolytic loss of a lipid side chain (molecular weight about 400 daltons); or (*c*) the addition of alcohols. The ability of an alcohol to disrupt the aggregate increases with its hydrocarbon content. From these data, it was concluded that lipid–lipid hydrophobic interactions are responsible for the self-association of diumycin. The aggregate is spherical with a mantle of hydrophilic sugars, including glucose and glucosamine, surrounding a tangle of lipid side chains (959).

The deuterium isotope effect on the biological activity of penicillin G was investigated by comparing the biological activity of the deuteriopenicillin with that of the protioanalog by a turbidimetric assay procedure using *S. aureus*. The biological assay indicated that a significant deuterium isotope effect operates in the antistaphylococcal action of benzylpenicillin. With the test organism chosen, the ratio of the antibiotic potencies was 125% H/D (960).

The pharmacokinetic profile of coumermycin A_1 was determined in man following intravenous and oral administration. The antibiotic was eliminated slowly from the bloodstream and appeared to be highly biotransformed. The plasma level *versus* time curve after intravenous injection was consistent with a two-compartment open system, containing a primary compartment with a volume equivalent to the volume of plasma water. The design of a pharmacokinetic model was discussed (961). As the free acid or simple salt, coumermycin A_1 is poorly absorbed from, and is not appreciably degraded in, the fluids of the gastrointestinal tract of animals and humans. A mixture of coumermycin with certain additives, such as sugar amines, can significantly enhance oral absorption in dogs, as indicated by the higher blood levels. With a mixture of antibiotic and *N*-methylglucamine in a 1:4 ratio, blood levels in both dogs and humans were enhanced 5- to 15-fold over that obtained with the antibiotic alone (962).

Additional references on antibiotics are found in Table XXVIII.

Table XXVIII—Additional References on Antibiotics

Reference	Topic
963	Increased absorption in dogs and humans after oral administration of coumermycin monosodium salt in a 1:4 w/w mixture with *N*-methylglucamine
964	Stabilities, modes of binding, and methods of disruption of aggregates of saramycetin and prasinomycin
965	Inhibitory effect of tetracyclines on rate of hydrolysis of an olive oil emulsion by pancreatic lipase
966	*In vitro* antibiotic activity of aminodeoxykanamycin
967	Stability of tetracycline hydrochloride in various ointment bases
968	Absorption, elimination, and *in vitro* sensitivity of *Pseudomonas pyocyanea* strains to carbenicillin
969	Hygroscopic and nonhygroscopic forms of oxytetracycline hydrochloride
970	Influence of storage conditions and pharmaceutical additives on stability of stamycin dragees
971	Influence of storage conditions on triacetyloleandomycin tablets
972	Metabolism of various antibiotics in hepatic dysfunction
973	Effect of adding bovine serum to various antibiotics on their *in vitro* bactericidal action
974	Review of polyene antibiotics and macrocyclic antibiotics and their effect on bilayer model membrane
975	Employment of hydron polymer antibiotic vehicle in otolaryngology
976	Biological activity of cephalexin in children
977	Pharmacokinetics of ampicillin and hetacillin
978	Stability of aqueous solutions of viomycin sulfate
979	Antibacterial activity produced in animals by coadministration of two antibiotics, demonstrating that the combination had significantly greater protective action than did individual components
980	Absorption, elimination, and metabolism of aminocyclohexylpenicillin
981	Review of structure–activity relationships of semisynthetic penicillins
982	Preparation of oxytetracycline in a dry powder for reconstitution

BIOPHARMACEUTICS

The various publications dealing with biopharmaceutics have been subdivided to aid the reader in locating areas of specific interest. Because of the obvious overlap in subject matter, the reader who needs a thorough review is advised to consider the entire section.

Schneller (983) reviewed the developments in biopharmaceutics with regard to the effectiveness of drug products. Included in his review is a table of 40 drug substances with proven, or definitely suspected, intrinsic susceptibility to bioavailability problems. The author noted that the subject of biological availability of a drug from its dosage form presents the pharmacist with challenges and opportunities which he is uniquely qualified to meet.

Numerous articles were published dealing with theoretical models as a means of correlating *in vitro* data with the therapeutic activity of a drug. The simultaneous chemical equilibria and mass transfer of basic and acidic drugs through a two-phase compartment model were theoretically investigated. The model consisted of a well-stirred bulk aqueous phase, an aqueous diffusion layer, and a lipid barrier for perfect and imperfect sink cases. The nonsteady- and quasi-steady-state changes in the concentration–distance distributions in the lipid phase were also considered. The rate of change of the total drug concentration in the bulk aqueous phase was described in the general form of a first-order equation useful for evaluating experiments. A limiting steady-state relationship involving the transport rate with the partition coefficient, pH at the aqueous–lipid interface, dissociation constant of the drug, aqueous and lipid diffusion coefficients, and thickness of the diffusion layer was derived. Increasing the agitation rate in the aqueous phase markedly affected the pH profiles for the rate of transport. The pH-partition theory was shown to be a limiting case of the more general approach presented (984).

In a similar study, multicompartment diffusional models for the absorption of neutral, acidic, basic, and amphoteric drugs were investigated. The general model consisted of a bulk aqueous phase, an aqueous

diffusion layer, *n*-compartments of homogeneous and heterogeneous phases, and a perfect sink. Equations were derived in general terms for the nonsteady- and steady-state periods. Utilizing the steady-state diffusion efficiency function of the barrier systems, the first-order rate constants for various examples of two- and three-compartment models were obtained from the general model, and some computations were given. Various sets of *in situ* experimental rat data were analyzed by means of the different models. These included the intestinal, gastric, and rectal absorption of sulfonamides and barbituric acid derivatives. Self-consistent dimensional constants and diffusion coefficients were arrived at, and the correlations obtained with the models were found to be generally satisfactory (985).

A general solution was presented for solving the pharmacokinetic parameters that describe a drug and its metabolite in a two-compartment open model. The method was specifically applied to the treatment of plasma data for acetylsalicylic acid and its metabolite, salicylic acid, after intravenous administration of the drug. The acetylsalicylic acid data were adequately described by a model in which elimination occurred solely from the central compartment (986). In the formulation of compartment models for describing biological phenomena, two separate approaches usually have been employed for isotope dilution systems and systems for which no tracers are introduced. For linear systems that can be described by first-order kinetics, it was shown that the isotope dilution problem can be cast into the more general approach by simultaneous linear differential equations, and the restriction of steady state can be removed. Solutions to these equations were shown to be easily obtainable, using the state-space approach. For systems in which linearity cannot be assumed, digital computer techniques were presented which greatly facilitated numerical solutions. These concepts were demonstrated with two examples, and a third example showed how these concepts and others could be employed with isotope dilution to find the initial pool sizes and rate constants in a six-compartment system (987). A six-compartment open-system model was presented to elucidate the physiological disposition of chlordiazepoxide and its two pharmacologically active biotransformation products by intravenous administration of the drug in dogs. The pharmacokinetic parameters used in the model were obtained by administering each of the three compounds separately. Excellent agreement was obtained between the levels of intact drug and the two metabolites found in the plasma of the dogs and the calculated levels of each generated from the model (988). A pharmacokinetic model was presented to describe the distribution of methotrexate in mice. The model was used to simulate methotrexate concentrations in plasma, lean tissue, liver, kidneys, and gastrointestinal tract following a single intravenous injection (989).

Loo and Riegelman (990) noted that if it is not feasible to administer a drug by a single bolus, it may be possible to administer the drug intravenously at a slower rate of infusion. A mathematical equation was presented which enabled one to determine the parameters identical to an intravenous bolus injection curve by utilizing the postinfusion blood curve. The equation is applicable to all compartmental models that may be described by linear first-order differential equations with constant coefficients. The transfer of salicylic acid and three sulfonamides from an aqueous phase of pH 2 or 5 through an intervening organic phase to an aqueous phase of pH 7.4 was studied, using a rotating cell. The manner of operation of the cell promoted rapid drug transfer without vortexation or emulsification of the phases. The rates of transfer of the drug showed the anticipated pH dependence (991). A transport cell was devised which consisted of three compartments, partitioned with two semipermeable cellulose membranes; the central compartment was thin and held a solution of nonpermeable material which acted as the barrier to drug transport. Transport of barbital and benzoic acid through the central compartment of aqueous polyvinylpyrrolidone was examined, and it was noted that the interaction of polyvinylpyrrolidone–benzoic acid was greater than that of polyvinylpyrrolidone–barbital, which consequently affected the transfer rates of these two drugs through the various compartments (992). A three-compartment *in vitro* transport model, consisting of two aqueous compartments buffered at pH 1.2 and 7.4 and separated by a thin, olive oil-impregnated Millipore membrane, was employed to study the transfer kinetics of four drugs in the absence and presence of the complexing agent caffeine. The apparent first-order transfer-rate constants obtained for salicylic acid, acetylsalicylic acid, dehydroacetic acid, and ethyl *p*-hydroxybenzoate correlated well with reported *in vivo* apparent first-order absorption-rate constants. In the presence of caffeine, the transfer rate of all of the drugs was significantly reduced, and calculated *in vitro* transport-rate constants were found to correlate well with reported *in vivo* absorption-rate constants for the drug–caffeine complexes (993).

For interpretation of blood concentration data to be meaningful, careful evaluation of the basic aspects of collection, description, and analysis of the data is essential. The importance of these considerations was illustrated by the magnitude of differences in rate constants obtained when the data were interpreted by different methods. The method of curve fitting presented minimized squared logarithmic deviations and offered a different approach by utilizing relative error rather than absolute error. The authors claimed that if truly equal weights are desired for data points, this is the more appropriate definition of best fit. In any case, however, no mathematical technique for fitting a model to the data can compensate for an inadequate description of drug activity (994). The concentration of drug in plasma after continuous administration has been defined as the relationship between dosage per unit time and the half-life of elimination to the volume of distribution. The plateau concentration determinants, elimination half-life, and volume of distribution were determined using a single-dose–continuous infusion technique. The data derived were used to predict the plateau concentration for a series

of substances administered by continuous intravenous infusion. Alterations in the volume of distribution and the elimination half-life of a drug may occur under clinical situations. This is reflected in changes in the plateau concentration, despite a constant dosage per unit time. An experimental example was described in which deoxycholic acid decreased the volume of distribution of bromsulfophthalein (995).

Additional references on biopharmaceutics are found in Table XXIX.

Effects of Physicochemical Properties—In addition to the effects of physical and chemical properties of a drug on its absorption, this section also includes references concerned with structure–activity relationships.

There is an often unrecognized distinction between the use of multiple-regression analysis as a predictive tool and as a means of investigating controlling physical characteristics in structure–activity studies. Three examples of complications that can arise with either of these applications were discussed. The first illustrates a "false" parabolic dependence of activity on lipophilicity; the second deals with unrecognized relationships between certain physical parameters; the third illustrates a situation wherein a number of statistically significant correlations can be presented, each of which may be given a different physical interpretation (1013). Using data previously reported, Martin (1014) pointed out the necessity of testing apparent structure–activity relationships with statistical methods. The inhibition potencies against *E. coli* W. of 11 structurally related tetracyclines, having a single substitution on the D ring, were correlated with substituent indexes, using three alternative analytical approaches. The *in vitro* activity of a compound not included in one of the analyses was predicted satisfactorily. The three approaches produced equivalent results, and correlations were applied to predict activities for tetracyclines having multiple substitutions on the D ring. Many of the predicted inhibition potencies against *E. coli* W. were of the same relative order of potencies as was observed when *S. aureus* was the test organism (1015).

Higuchi and Davis (1016) presented a new quantitative and comprehensive approach relating structures of congeneric drugs to their relative biological activities. The analysis was based on the assumption that changes in structure affect a large number of time-dependent processes, such as the absorption, transport, transformation, and excretion of a drug, and that it appears highly unlikely that any single relationship accounts for all structure–activity relationships. Relationships under equilibrium or quasiequilibrium conditions were considered, thus permitting rigorous thermodynamic treatment. On the basis of the effect of structural changes on the distributive tendencies of the drug in various body tissues, including the receptor site, relationships were derived which are, surprisingly, in good agreement with available experimental data. The approach suggested a rational way to predict the degree of lipophilicity that would result in maximal activity. Based on experimental observation that concentrations of ionized and unionized molecules of sulfonamides at the bacteriostatis are linearly related to the drug's pKa, equations of the relation of pKa to bacteriostatic activity of sulfonamides against *E. coli* were proposed; the optimal pKa of sulfonamides, which are active at a minimum concentration, was calculated (1017). In a similar article, the Hansch–Fujita equation was applied to an analysis of the natriuretic activity of sulfonamide carbonic anhydrase inhibitors, using certain hydrophobic and electronic parameters. Sixteen benzenesulfonamide derivatives were satisfactorily applied to the structure–activity analysis of heterocyclic sulfonamides. It was concluded that a strong natriuretic activity was observed for sulfonamides, which had an optimal hydrophobicity and low electronegativity at the sulfamoyl groups or a strong inhibitory activity against carbonic anhydrase (1018).

The apparent partition coefficients of 48 alkylsulfates of substituted quinolinium compounds and 19 alkylsulfates of substituted pyridinium derivatives were correlated with Bondi's group contribution to the surface area, Hansch's π constant, and Hammett's σ constant. The surface area of the ring substituent and the alkyl group appeared to be the most important factors governing the apparent partition coefficient (1019). Substitution of a methyl group at one or both of the *ortho*-positions of the benzene ring in procaine amide and procaine provided analogs that were more active in prolonging the refractory period of isolated rabbit atria than procaine amide itself. Reversal of the amide in procaine amide significantly reduced the activity by prolonging the refractory period of cardiac

Table XXIX—Additional References on Biopharmaceutics

Reference	Topic
996	Comparison of *in vivo* and *in vitro* absorption from gastrointestinal tract
997	Rank-order correlations of *in vivo* data with *in vitro* rate of dissolution, showing the variety of *in vivo* parameters employed in correlations and the many different types of *in vitro* tests employed to obtain *in vitro* parameters
998	Influence of dissolution rate of sulfadimidine tablets on absorption and excretion, using a urinary excretion method
999	Biomedical model for absorption studies from various gastrointestinal sites in dogs
1000	Correlation between *in vitro* disintegration tests and therapeutic efficacy of compressed pharmaceutical tablets
1001	Relation between drug solubility in lipids and their pharmacokinetic behavior
1002	Review of physicochemical parameters in drug design
1003	Generalized solution to linear two-compartment open model for drug distribution
1004	Pharmacokinetic model of elimination of endogenous substances such as bilirubin, iron, and glucose
1005	Pharmacokinetic studies in animals as model systems for human therapy
1006	Biopharmaceutical and pharmacokinetic aspects of drug safety and efficacy
1007	Transfer and transit as pharmacokinetic relations in a multicompartment model
1008	Lipid models of drug resorption, permeation, and penetration
1009	Review of pharmaceutics, pharmacokinetics, and biopharmaceutics
1010	Physicochemical parameters in drug design
1011	Gastrointestinal bleeding resulting from oral administration of aspirin not due to precipitation of a protective glycoprotein component of gastric juice
1012	Evaluation of the dog as an experimental model for study of insulin distribution and degradation in man

Table XXX—Additional References on the Influence of Physicochemical Properties on Drug Absorption

Reference	Topic
1021	Benzoic acid being percutaneously absorbed at 200 times the amount of its glycine conjugate, hippuric acid; nicotinic acid being insignificantly penetrated, with 10% of its amide, nicotinamide, being absorbed; suggesting that molecules may be tailored to decrease or increase penetration as needed for the most suitable biological function
1022	Relationship between lipophilic character and biological activity of cephalosporins and penicillins suggesting certain structure–activity correlations
1023	Relation of structure to the bacteriostatic activity of sulfonamides using Hansch's hydrophobicity constant
1024	Soluble methylprednisolone sodium succinate being effective more rapidly in clinical conditions responsive to steroids than the less soluble methylprednisolone acetate
1025	Potassium ampicillin being absorbed more rapidly and achieving higher peak blood levels than the trihydrate form
1026	Species differences in absorption, metabolism, and excretion illustrated by psychoactive drugs from the dibenzobicyclooctadiene series
1027	Importance of cationic charge and steric factors on cholinergic properties of three noracetylcholine derivatives
1028	Pharmacodynamic evaluation of an acetylenic derivative of gallamine
1029	Pamoates, a class of oral drugs with delayed and prolonged effects
1030	Steric models of drugs for prediction of psychedelic activity
1031	Differences in human blood levels after administration of two different L-asparaginases
1032	Importance of guanido group in position 4 and the influence of the isopropyl group in position 13 for antibacterial activity of dehydroabietylamine derivatives
1033	Review of structure–activity relationships of five tetracycline antibiotics
1034	Review of problems of establishing structure–activity relationships in drug research
1035	Molecular approach to modulation of pharmacokinetics and modification of metabolic conversion by molecular manipulation
1036	Molar attraction constants applied to structure–activity relationships
1037	Correlation between activity and electronic state of hallucinogenic amphetamines

tissue and did not seem to improve the antiarrhythmic activity of the parent compounds (1020).

Additional studies describing the influence of physicochemical properties on drug absorption are provided in Table XXX.

Effects of Formulation—The effects of different vehicles on excretion and metabolism of serotonin and imipramine were studied. Rats receiving labeled serotonin in dimethyl sulfoxide or propylene glycol excreted radioactive material in the urine slower and in lesser amounts when water was the vehicle. Dimethyl sulfoxide and propylene glycol not only caused an increase in the amount of urinary 5-hydroxytryptophol and *N*-acetylserotonin but also in the conjugated form of these two metabolites as well as that of 5-hydroxyindoleacetic acid. The two nonaqueous vehicles also caused a diminished demethylation of imipramine compared with the water vehicle (1038).

The highest blood levels of both phenacetin and free acetaminophen were observed after oral administration of a fine particle-size suspension of phenacetin with polysorbate 80 (Tween 80), followed, in decreasing order, by a fine particle-size suspension without polysorbate 80, medium particle-size suspension, and coarse particle-size suspension. This indicates that particle size is an important factor in absorption of phenacetin and that the absorption is apparently enhanced by polysorbate 80 (1039). Sodium deoxycholate markedly enhanced the absorption of phenol red in the rat by altering the permeability of the intestinal membrane. While this was true for the isolated everted rat intestine, in the intact rat these effects appeared to be reversible (1040). Certain surface-active agents placed in a Thomas canine fundic pouch in buffered solutions influenced the absorption of soluble antibiotic drugs. Such agents induced a rapidly reversible hyperabsorptive state of the organ, resulting in blood levels of absorbed drug many times greater than control values. The influence of the surface-active agent, be it nonionic, anionic, or zwitterionic, is upon the organ and not upon the drug, as evidenced by the efficiency of the absorption promoter when it is employed and removed before the drug is introduced (1041). Low concentrations of polysorbate 80 and oleic acid, which enhance drug absorption across the external membranes of goldfish, have no apparent effect on the absorption of salicylate, salicylamide, and 4-aminoantipyrine from the *in situ* rat small intestine (1042).

Below the certain critical concentration of polysorbate 80, the activity of chlorpromazine hydrochloride in solution in goldfish was enhanced in unbuffered drug solutions. Above this concentration, the activity was diminished, possibly due to some association between surfactant micelles and drug molecules. The rate of solution of chlorpromazine hydrochloride from coated tablets was increased in 2% aqueous polysorbate 80, but the activity was decreased compared with that in a simple aqueous dissolution medium, thus providing direct evidence of the erroneous conclusions that can be obtained if dissolution measurements alone are used in assessing the effect of additives on drug performance (1043).

The rectal absorption of aspirin, aluminum aspirin, and calcium carbaspirin was studied in dogs using bases of cocoa butter, polysorbate 61, polyethylene glycol mixture, and a mixture of natural saturated vegetable fatty acid glycerides. The absorption of aluminum aspirin from cocoa butter and the polyethylene glycol mixture was poor. Plasma salicylate levels from aspirin and calcium carbaspirin in the polysorbate 61 base were minimal. The greatest absorption was seen with calcium carbaspirin in vegetable fatty acid glyceride base. The authors could draw no conclusions regarding any differences in absorption of aspirin or calcium carbaspirin in the various bases or the commercial aspirin product (1044). Different oral dosage forms of griseofulvin were administered to dogs; absorption was complete for griseofulvin dissolved in polyoxyethylene glycol 400, 88% complete when dispersed in polyoxyethylene glycol 6000 contained in a capsule, 45% complete for the commercial capsule, and 33% complete for the commercial tablet (1045).

An insoluble drug–polysalt complex of chlorpromazine hydrochloride, sodium carboxy methylcellulose, and protamine sulfate was selected as a model to evaluate the effects of these macromolecular constituents on the *in vitro* and *in vivo* availability of the interacted

drug. The *in vitro* drug-release studies suggested that the product possesses prolonged-release properties, while the *in vivo* studies with rats revealed a promoted bioavailability of the drug in the presence of the polysalt complex. Protamine sulfate, a known pinocytotic inducer, was specifically implicated in this phenomenon (1046). By using a prebuffer technique or by adding buffer and/or viscolizer to certain dilute mydriatic solutions, similar physiological effects were obtained as were by using unbuffered solutions 10 times more concentrated. The addition of 0.5% hydroxypropylmethylcellulose, 4000 cps., to buffered mydriatic solutions did not further increase the pupil size of Caucasians, compared with the effects from the same buffered solution without viscolizer; a more marked dilating effect was produced in the pupils of Orientals (1047).

Additional studies on the effects of formulation on drug absorption are provided in Table XXXI.

Absorption Control and Alteration—This section of biopharmaceutics considers articles dealing with absorption control and alteration as influenced by the coadministration of drugs, disease, blood flow, fasting, route of administration, and age.

The effects of six parameters on the physiological availability of orally administered griseofulvin formulations were studied by the use of urinary metabolite excretion data from a single subject. The first parameter, time of administration, had an effect on absorption in the manner of a circadian rhythm, the absorption being least in the morning and maximum at noon. The second parameter, high-fat meal, appeared to be equivalent to a delay in administration; consequently, its effect depended on the previous factor. The third parameter, dosage, indicated that the percentage absorption of drug was independent of the amount administered. The fourth parameter, particle size, showed that twice as much micronized griseofulvin was absorbed as nonmicronized griseofulvin. The fifth parameter, dissolution rate, had little effect on absorption as long as the dissolution rate was above a given value. The sixth parameter, gastrointestinal transit time, could not be varied enough by dietary means except in the cases of greasy fried foods and nuts, to affect significantly the residence time of griseofulvin at the absorption sites (1080).

The effect of probenecid on the renal clearance of riboflavin was determined in three human subjects at various serum concentrations of the vitamin. Renal clearances of riboflavin exceeded the endogenous creatinine clearances, which indicated that riboflavin excretion involved renal tubular secretion. The clearance of riboflavin was less at low than at high serum concentrations of the vitamin, which is characteristic of a saturable tubular reabsorption process. Probenecid decreased the renal clearance of riboflavin, and this effect was directly related to the serum concentration of the inhibitor, The serum protein binding of the vitamin was essentially constant over the concentration range encountered and was unaffected by the presence of probenecid (1081). Pretreatment with heptabarbital had no effect on prothrombin complex activity before warfarin administration and did not affect the apparent first-order rate constant for prothrombin complex activity degradation or the relationship between plasma warfarin concentration and prothrombin complex activity synthesis rate. The decreased response to warfarin during barbiturate administration was, therefore, due only to the inductive effect of the barbiturate on the warfarin-metabolizing enzyme system. There was no evidence that the barbiturate affected the distribution of warfarin in the body, the inherent ac-

Table XXXI—Additional References on Effects of Formulation on Drug Absorption

Reference	Topic
1048	Blood levels of chlorphentermine in man after oral administration of the drug in solution, as a prolonged-release formulation, and as an intravenous injection
1049	Review of mechanisms of surfactant effects on drug absorption
1050	Absorption of acetylsalicylic acid from unbuffered and buffered gastric contents
1051	Influence of dimethyl sulfoxide on percutaneous migration of potassium dodecyl sulfate
1052	Review of the role of surface-active agents in drug absorption
1053	Extent of *in vivo* absorption of insoluble streptomycin in various suppository bases
1054	Release of sulfonamides from certain ointment bases
1055	Effect of syrup on the absorption of drugs from gastrointestinal tract
1056	Relation between percutaneous absorption and stratum corneum retention of drugs
1057	Percutaneous absorption of certain corticosteroid hormones
1058	Dimethyl sulfoxide markedly increased the diffusion rate of tritiated water through human abdominal autopsy skin
1059	Effect of dimethyl sulfoxide on absorption of iron applied to piglets
1060	Effect of excipients on appearance of xanthotoxin erythemia in guinea pigs upon irradiation
1061	Effects of surfactants and solvents on permeability of epidermal tissue
1062	Factors affecting drug concentration delivered from nasal inhalers, noting the importance of studying vapor pressure characteristics of the volatile drug
1063	Effect of tablet dosage form on absorption of aspirin
1064	Comparison of profiles of gastrointestinal absorption of theophylline from various vehicles
1065	Salicylate blood levels in rabbits after oral administration of aspirin in different dosage forms, showing phosphate increasing the rate of absorption
1066	Comparison of blood levels after administration of theophylline in tablet and liquid dosage forms
1067	Factors influencing release of active substances from suppositories, demonstrating advantageous effects of surfactants
1068	Influence of tablet, suspension, and syrup dosage forms on absorption of tetracycline
1069	Review of significance of particle size in relation to drug absorption
1070	Urinary elimination of micronized and crystalline nitrofurantoin, showing the micronized form is excreted more rapidly
1071	Difference in intestinal absorption of acetylsalicylic acid in dogs due to particle size
1072	Review of influence of formulation on drug action
1073	Dependence of biological activity on the degree of dispersion, showing intensity and duration of drug action are a function of particle size
1074	Review of formulation factors influencing therapeutic effect of pharmaceuticals
1075	Review of effects of pharmaceutical formulations on biological actions of drugs
1076	Effect of compression pressure on the activity of anti-inflammatory enzyme tablets
1077	Effect of various suppository bases on rectal absorption of choline salicylate in the rabbit
1078	Effect of eye drop adjuvants on the responses of human eye to some autonomic drugs
1079	Diazepam blood levels after administration as solution or syrup

tivity of the blood coagulation process, or the response of the appropriate receptor to warfarin (1082).

The absorption rate of taurine and glycine in the presence and absence of aspirin was examined in the rat digestive tract. Neither was absorbed in the stomach, either alone or with aspirin. Alone, both were absorbed to a certain extent from the small intestine, but glycine behaved differently when aspirin was present; that is, taurine was absorbed alone and in the presence of aspirin, and the absorption of glycine was increased in the presence of aspirin. These results indicate that neither compound is absorbed in the stomach, but both promote the absorption of aspirin from the stomach and the small intestine as they themselves are being absorbed. In the small intestine, absorption of glycine seems to be accelerated by aspirin (1083). In the presence of tetracycline, sulfanilic acid disappeared faster from the small intestinal recirculating solution at pH 8.0. At pH 6.0, however, this absorption enhancement was not observed. In the presence of tetracycline, the blood level of sulfanilic acid increased at pH 8.0 but not at 6.0; this result agreed with that obtained from the intestinal recirculation method. These results suggest that the increased absorption of sulfanilic acid is not due to complex formation with tetracycline in the gut lumen but to the direct effect of tetracycline on the absorptive membrane (1084).

Walker (1085) studied the influence of protein binding on the excretion of some sulfanilamidopyrimidines in man. The plasma protein binding data included the percentage bound at various concentrations of the drugs, the number of binding sites, the binding capacity of plasma albumin, and the dissociation constant of the sulfonamide–albumin complex. It was noted that the short-acting sulfasomidine was bound to a much lesser extent, at the concentration obtained clinically, in the plasma than the long-acting sulfa drugs. In addition, sulfasomidine occupied only one binding site on plasma albumin, while the other sulfonamides occupied two sites. This may partly account for the rapid excretion of sulfasomidine in man. Absorption rates of carbazochrome and nicotinamide in the presence of caffeine and hydroxyethyltheophylline were determined to ascertain whether the increase or decrease of absorption rate in the presence of the complexing agent was due to the intraluminal complex formation. The results suggested that the effect of caffeine and hydroxyethyltheophylline on the absorption rate of the drug was apparently due to complex formation (1086). Complexation influence on the rate of absorption of actively transported drug was investigated in the perfused small intestine, employing L-tryptophan as a model drug and caffeine, 8-chlorotheophylline, 8-methoxycaffeine, 7-hydroxyethyltheophylline, and flavin mononucleotide as complexing agents. Flavin mononucleotide reduced the rate of absorption of L-tryptophan—not by directly affecting the absorptive membrane or by impairing the neutral amino acid transport system but by decreasing the thermodynamic activity of L-tryptophan resulting from molecular complexation with flavin mononucleotide in solution (1087).

Nondissociable substances such as tritiated water, methanol, ethanol, urea, ethylene glycol, glycerol, and erythritol showed increased absorption rates as the intestinal blood flow in rats increased (1088). Similarly, by using sulfaethylthiadiazole in dogs, it was confirmed that the intestinal drug absorption process is hindered by a decrease in vascular profusion (1089). Chung *et al.* (1090) showed that cations play a definite role in the transport of weak organic acids in the rabbit kidney slice, although the mechanisms of action are entirely unknown at present. Dose for dose, the concentration in blood and the urinary excretion rate of pentazocine are much lower after oral than after intravenous administration (1091). Absorption of D-glucose and 3-*O*-methylglucopyranoside was enhanced significantly in both short-term and long-term alloxan diabetes, while active transport of both monosaccharides was increased by fasting for 24–72 hr. (1092).

To exclude the effect of probenecid on renal excretion, the distribution and elimination of riboflavin with and without probenecid were studied in two functionally anephric patients during hemodialysis. Using a two-compartment open model, a pharmacokinetic analysis was made of the time course of the plasma levels of the vitamin. Probenecid had no appreciable effect on the distribution- and transfer-rate constants of riboflavin. Riboflavin was eliminated more slowly by hemodialysis of the patients than by renal excretion in normal subjects (1093). The development of gastrointestinal absorption function in humans was studied using riboflavin, which is absorbed by a site-specific and saturable transport process. The urinary recovery of the vitamin ranged from 6 to 12% of the dose in subjects ranging in age from 3 months to 40 years, respectively. The kinetics of riboflavin elimination were independent of age. These observations suggest that in the age range studied, younger subjects retain the vitamin at intestinal absorption sites for a shorter period than do older subjects, due to a decreased intestinal transit rate with increasing age. Therefore, prompt release of drugs from pharmaceutical dosage forms seems even more important in children than in adults to assure adequate absorption (1094).

After administration of 20 mg. of thiamine hydrochloride, a maximum of 4.77 mg. was absorbed in normal subjects, whereas only 1.5 mg. was absorbed in malnourished alcoholic patients with fatty liver or cirrhosis. Ethanol, given either parenterally or orally, caused a 50% reduction in thiamine absorption in 4 of 12 alcoholic patients without liver disease (1095).

Additional studies on absorption control and alteration are given in Table XXXII.

Absorption Mechanism—Mechanisms of intestinal salicylamide glucuronide formation and transport were studied in the rabbit *in vitro* with cannulated everted intestines and *in vivo* with perfused and closed intestinal loops with complete mesenteric venous blood collection. Both techniques indicated that glucuronide formation is capacity limited when the lumen concentration exceeds 10^{-3} *M*. The appearance of glucuronide across the basal barrier is limited by the transport step rather than by the rate of glucuronide synthesis, leading to accumulation of the compound in the tissue compartment (1146). There are three likely mechanisms by which bile salts can affect the absorption from the rat small

Table XXXII—Additional References on Absorption Control and Alteration

Reference	Topic
1096	Drug absorption as affected by interactions mediated by binding displacement, changes in drug metabolism, interactions at specific sites of drug action, and interactions which affect drug excretion
1097	Effect of phenobarbital on disappearance of diphenylhydantoin from serum of children
1098	Enhanced penetration of testosterone by dimethyl sulfoxide through the stratum corneum of human skin
1099	Absorption and topical distribution of oxytetracycline in healthy and experimentally infected animals
1100	Increased absorption of prednisone from rat intestine using *N,N*-di-*n*-propylpropionamide
1101	Review of the effect of food on drug absorption
1102	Rate of absorption of oral thyroxine appearing to be as rapid in hypothyroid patients as in normal patients
1103	Effect of dose and sodium and potassium concentration on the absorption of digoxin from the perfused intestinal loop of the rat
1104	Comparative studies on cephaloridine and cephalothin in patients with renal insufficiency treated with or without dialysis
1105	Serum and liver levels of vitamin A after a single massive dose
1106	Effect of chlorpromazine on disposition and excretion of amphetamine in the rat, suggesting that chlorpromazine impairs the hydroxylation of amphetamine supposedly at the level of liver microsomes
1107	Mechanism of action of accelerants on skin penetration, using urea and dimethyl sulfoxide
1108	Influence of drugs on tissue permeability
1109	Comparative elimination of glyceryl guaiacol administered rectally and cutaneously as an ointment
1110	Review of reduced action of drugs in combination
1111	Effect of phenobarbitone pretreatment on the metabolism of neostigmine *in vivo* and *in vitro*
1112	Paired comparisons of absorption between three topically applied drugs
1113	Enzyme induction by drugs in humans, resulting in increased metabolism and lower blood levels
1114	Physiological factors affecting intestinal drug absorption
1115	Serum concentration and urinary excretion of ouabain and digitoxin in patients suffering from hyperthyroidism or hypothyroidism
1116	Inhibition of subcutaneous absorption in rats by local anesthetics
1117	Review of drug latentiation
1118	Review of enhanced action of drugs in combination
1119	Inhibition of activity of isoniazid in the presence of chloroquine diphosphate
1120	Evidence for significant nonperipheral effects of phenformin on glucose metabolism in normal subjects, suggesting that phenformin inhibits intestinal absorption of glucose
1121	Effect of phenobarbital on plasma disappearance and biliary excretion of drugs in rats
1122	Pharmacokinetics of *N*-acetyl-*p*-aminophenol as affected by phenylbutazone
1123	Review of interactions of drugs with other drugs or other therapeutic devices
1124	Malabsorption due to effect of paromomycin on protein synthesis in the small intestine
1125	Effect of 2-diethylaminoethyl-2,2-diphenylvalerate hydrochloride on drug concentration in the blood
1126	Effect of bile salts on calcium absorption
1127	Effect of antibiotics on hexobarbital sleeping time in rats
1128	Influence of magnesium and some other divalent cations on hepatic microsomal drug metabolism *in vitro*
1129	Synergistic effect noted when sulfamethoxazole and trimethoprim are combined in treatment of gonorrhea
1130	Synergism of tetracycline and amphotericin B *in vitro*
1131	Increased ileal absorption of salicylic acid induced by carbonic anhydrase inhibition
1132	Altered absorption of drugs from the rat small intestine by carbonic anhydrase inhibition
1133	Inhibition of tolbutamide decomposition in man by sulfaphenazole
1134	Inhibition of binding of glycine to rat brain cortex membrane by strychnine
1135	Increased urinary salicylate excretion in rats following administration of acetylsalicylic acid in combination with glucuronamide
1136	Drugs, toxins, and dietary amino acids affecting vitamin B_{12} or folic acid absorption or utilization
1137	Ineffectiveness of succinic acid and ascorbic acid in increasing the absorption of iron from a tablet dosage form
1138	Influence of succinic acid on absorption of iron studied by whole-body monitoring; iron utilization not being increased by addition of free succinic acid
1139	Review of the pharmaceutical and absorption aspects of drug interactions
1140	*In vitro* changes of the serum binding capacity of insulin-^{131}I under influence of tolbutamide and glybenclamide in normal subjects, young and old diabetics, and in insulin resistance
1141	Alterations in deoxyribonucleic acid (DNA)-bound amino acids after the administration of DNA-binding drugs
1142	Effect of administering other drugs during oral anticoagulant therapy
1143	Review of substances that facilitate sorption of pharmaceuticals by the skin
1144	Effect of renal insufficiency on behavior of deoxycycline
1145	Interactions between sympathomimetic amines and a monoamine oxidase inhibitor, showing marked potentiation of certain physiological properties of the amines

intestine: (*a*) the loss of thermodynamic activity of a drug due to the formation of the micellar complex, (*b*) the local concentration buildup effect such as an accumulation on the absorptive surface, and (*c*) the direct effect on the permeability characteristics of the intestinal mucosa (1147). Warfarin was eliminated more rapidly, but its anticoagulant effect was increased by concomitant administration of phenylbutazone. Pharmacokinetic analysis showed that the prewarfarin synthesis rate and the normal degradation of prothrombin complex activity are not affected by phenylbutazone, but this drug has a pronounced effect on the relationship between the synthesis rate of prothrombin complex activity and plasma-warfarin concentration. These observations are consistent with the assumption that phenylbutazone competitively displaces warfarin from nonspecific binding sites in the plasma and tissues and thereby increases the interaction of the anticoagulant with its pharmacologic receptor and metabolizing enzyme system (1148).

It was demonstrated that in the very early stage of drug absorption, vitamins solubilized in micelles are adsorbed onto the membrane, which are favored by the surface-active agent; in the slow phase, absorption now becomes rate limited by the partition or release of the vitamins from adsorbed micelles to the mucosal layer of the membrane (1149). The distribution and metabolism of vitamin K and warfarin were studied in the warfarin-resistant rat. The data obtained were consistent with the hypothesis that warfarin resistance results from a mutation that caused the synthesis of a protein with a lowered binding affinity for both vitamin K and its antagonist, warfarin (1150).

The demonstration that a capacity-limited system for acetylation of sulfanilamide exists in the rat is important for drug metabolism studies in this species but may not

Table XXXIII—Additional References on Mechanisms of Absorption

Reference	Topic
1155	Metoclopramide-N^4-glucuronide may be absorbed from the intestine not only in the parent compound, namely, metoclopramide, resulting from hydrolysis but in the intact form as well as the sulfonate
1156	Elucidation of mechanism of change of methanesulfonated drug *in vivo* on derivatives of substituted anilines
1157	Mechanism of inhibition of *in vitro* glucose transport by oral administration of phenformin HCl
1158	Review of stimulation and inhibition of drug metabolism
1159	Mechanism of abnormal response to oral metyrapone showing absorption and conjugation of metyrapone during diphenylhydantoin therapy
1160	Inhibition of protein synthesis as a mechanism for interfering with intestinal lipid transport
1161	Differences in the rate of biotransformation of glyceryl guaiacolate to inactive products being responsible for half-life differences of this drug in stallions and mares
1162	Degree of protection to the convulsant action of metrazole being most closely related to the rate of disappearance of the *N*-demethyl derivative
1163	Review of factors that permit availability of a drug to the absorption site in a complex organism
1164	Demonstration of a nonsaturable transport process for intestinal absorption of tritiated ouabain

be necessarily relevant to man. Based on experimental data obtained, it was concluded that drug metabolism studies must be carried out at multiple-dose levels and that the linearity of the semilogarithmic plots of drug elimination as a function of time is frequently insufficient to discriminate between dose-independent or dose-dependent biotransformations (1151). It was found that the cause of the poor absorbability of sulfaguanidine could not be attributed to its dimer formation or to the iceberg formation in aqueous solution. Since bile salts did not affect the physicochemical properties of sulfaguanidine, such as apparent partition coefficient and diffusion constant, and did not form a micellar complex with the drug, it was evident that the absorption enhancement was not caused by their intraluminal effect. On the absorptive surface, bile salts did not increase the affinity of the sulfa drug for the intestinal mucosal surface. An exsorption study demonstrated that such enhancement was caused by the direct action of bile salts on the structure of the absorptive surface (1152).

A micropuncture study of the effects of urea infusion on tubular reabsorption in the rat indicated that, at the plasma levels achieved in the study, urea did not significantly decrease water and solute reabsorption in the proximal convolutions but did inhibit water, but not sodium, reabsorption in the more distal portions of the nephron (1153). In a study of the *in vitro* human percutaneous penetration and epidermal-dermal retention of benzyl alcohol and testosterone, it was suggested that the dermis may exhibit a role in the retention and penetration of these chemicals (1154).

Additional references on the mechanism of absorption are provided in Table XXXIII.

Drug Absorption—Two experimental methods for use in kinetic studies on a compartment model for intestinal metabolism and absorption were evaluated. The *in vitro* cannulated everted intestinal sac and the *in vivo* intestinal loop with complete mesenteric venous collection were compared in the same region of rabbit intestine. These methods were used to study the effects of blood flow on the transport of salicylamide across the basal barrier and to provide experimental evidence to support the cell compartment model. The rate of transport of free drug across the basal barrier is blood flow rate limited, while the transport of glucuronides is essentially independent of blood flow. There was a lag time of 4 min. in the appearance of free salicylamide into mesenteric blood *in vivo* and a lag time of about 10 min. into serosal fluid *in vitro*. The steady-state rate of appearance of free drug into the plasma, *in vivo*, was 5–10 times greater than the rate of appearance of free drug into the serosal fluid at similar mucosal concentrations. The *in vivo* intestinal loop with complete venous collection provided many advantages in studying physiological factors of intestinal drug absorption (1165).

Diffusion rates of fatty acid in bile salt solution and in polyoxyethylene–polyoxypropylene copolymer solution depended on the amount of fatty acid solubilized and also on any physical restrictions to flow. Micelles of the two types of surfactant were significantly different in size. Assuming a passive process for the uptake of fatty acid, diffusion rates correlated with the observed uptake of fatty acid into the everted intestinal sac of the rat (1166).

Clindamycin, which is known to be absorbed from the gastrointestinal tract, was absorbed extremely slow, or possibly not at all, from the buccal cavity at various pH values. This finding indicated that buccal absorption alone cannot be used to predict the gastrointestinal absorption of a compound (1167).

A comparison was made of the gastric absorption and distribution of tritiated sodium acetylsalicylate with the absorption and distribution of sodium salts of other weakly acidic compounds. Each of the other compounds has a characteristic absorption pattern. Only sodium acetylsalicylate caused gastric lesions in the rat. These observations do not rule out the possibility that the absorption characteristics of acetylsalicylic acid and its salts may be associated with their ability to cause gastric ulcers (1168).

A simple method for the detection of chromonar and its acid metabolite by fluorescence techniques was described. Following oral or intravenous administration, chromonar was rapidly hydrolyzed to its acid metabolite. The metabolite distributes according to a single-compartment model; the plasma half-life is 1 hr. in man and dog. Excretion of the metabolite into the bile accounts for approximately 25% of the dose, and excretion into the urine accounts for the remainder (1169).

Blood concentrations of carbenoxolone generally exhibit two maxima: at 1–2 and 3–6 hr. after dosage. Because absorption of orally administered drug is so rapid and does not occur when the gastric contents have a pH greater than 2, it was inferred that the major site of absorption is the stomach. The high blood concentrations of carbenoxolone are probably due to a high degree of binding of the drug to plasma proteins. Gastric absorption of the drug may be necessary for the increased production of gastric mucus and, hence, for gastric ulcer-healing activity (1170).

Additional references on drug absorption are provided in Table XXXIV.

Pharmacokinetics—It was shown from apparent first-order urinary excretion studies with D-(−)-mandelic acid and certain of its homologs, DL-tropic acid, D-(−)-4-hydroxy-4-phenylbutanoic acid, DL-phenyllactic acid, and D-(−)-benzyllactic acid, that the biological half-lives of the homologs are significantly shorter than the half-life of D-(−)-mandelic acid in rats. Since these compounds, which differ from each other in their content of methylene groups around the carboxyl group, exhibit negligible metabolism and protein binding, low pKa values (3.3–4.7), and low lipid solubility at the physiological pH, and are recovered primarily in the urine in the intact form, they were utilized to study the effect of hydrophobic group(s) on the rate of secretion. The compounds exerted a mutual inhibitory effect on their renal tubular secretion, indicating a common "carrier" mechanism for their secretion. The addition of methylene group(s) in the vicinity of the carboxyl group of the mandelic acid molecule increased its affinity for the carrier molecules of the renal tubular secretion system in rats (1194). From the pseudo-first-order urinary excretion studies of D-(−)-mandelic acid and DL-tropic acid in rats, data regarding the apparent initial secretion rate *versus* dose (intravenous) were obtained and treated according to Michaelis–Menton kinetics. Although the maximum apparent initial secretion rate determined for these compounds was similar, the amount of substrate required to produce one-half the maximum apparent initial secretion rate determined for D-(−)-mandelic acid was found to be about twice that determined for DL-tropic acid. Data were obtained to demonstrate that these compounds competitively inhibit the renal tubular secretion of each other, thereby strongly indicating that these compounds share a common carrier transport system for their secretion. Data obtained in these studies and those described earlier were utilized to distinguish a certain structural characteristic around the cationic site of the "carrier" molecules of the renal tubular secretion system in rats (1195). The kinetics of metabolism and urinary excretion of the optical isomers of mandelic acid were studied in three human subjects. The rate constants were determined for a model consisting of parallel apparent first-order processes for excretion of intact mandelic acid and metabolism to benzoylformic acid. The kinetic studies revealed no significant difference in the rate of urinary excretion of L-(+)- and D-(−)-mandelic acid, but there was a difference in the metabolic metabolism of these two isomers in the subjects. The rate constant for metabolism of L-(+)-mandelic acid was approximately twice that for the metabolism of D-(−)-mandelic acid. The inhibitory effect of probenecid on the urinary excretion of the optical isomers of mandelic acid suggests that both isomers are involved in the active renal tubular secretion (1196).

Pharmacokinetic relationships were developed to characterize a multicompartment drug distribution and elimination model, which included a saturable renal tubular reabsorption process. The derived expressions were applied to serum concentration and urinary excretion data obtained after rapid intravenous administration of riboflavin to man and dog. The mathematical relationships and experimental data demonstrate the dependence of renal clearance on the serum concentration of the drug and on urine flow rate. The results of this study indicate that the renal excretion of riboflavin, like that of several other water-soluble vitamins, involves saturable tubular reabsorption as well as tubular secretion (1197).

The steady-state growth of *E. coli* in broth cultures was inhibited by erythromycin with a new steady-state growth-rate constant that was linearly related to drug concentrations in the range 0–10.0 mcg. ml.$^{-1}$. The growth-rate constant at drug concentrations greater than 10 mcg. ml.$^{-1}$ adhered to a kinetic model, which implies the saturation of a limited number of receptor sites in accordance with an equation. The dependence of *E. coli* growth rate on drug concentrations was invariant with the organism population or broth concentrations. However, values of k_a increased 10-fold as the pH of broth was increased from 6.8 to 7.8, while k_0 remained constant. This indicates that the unprotonated fraction of the drug concentration contributes to the activity. Lincomycin in Phase I-affected growth

Table XXXIV—Additional References on Drug Absorption

Reference	Topic
1171	Absorption, distribution, excretion, and metabolism of oxymethebanol
1172	Absorption of ^{64}Cu from the gastrointestinal tract of the rat
1173	Effect of pH of solution on percutaneous absorption of acidic and basic drugs
1174	Laboratory experiment demonstrating percutaneous absorption
1175	Intestinal absorption of cardiac glycosides by measurement of tritiated glycosides in the blood of the portal vein and in the intestinal lymph
1176	Investigation of percutaneous absorption of antibacterial agents
1177	Evaluation of drug absorption by measurement of urinary excretion
1178	Laboratory experiment demonstrating *in vitro* release of medicament from ointment bases and its application to drug absorption
1179	Oral absorption and disposition kinetics of lidocaine hydrochloride in dogs
1180	Percutaneous absorption of antibacterial substances
1181	Review of factors affecting gastrointestinal absorption of drugs
1182	Effect of various cations on the passive transfer of drugs across everted rat intestine
1183	Intestinal absorption of tritiated chymotrypsin in dogs
1184	Local and systemic absorption, excretion, and tolerance of clindamycin hydrochloride after intramuscular administration
1185	Review of absorption after oral administration of drugs in sustained-action dosage forms
1186	Relation between clinical effects of lithium and its absorption, distribution, and excretion
1187	Methods for measuring cutaneous permeability
1188	Absorption and excretion of tritiated dihydrostreptomycin in cattle and swine
1189	Blood levels and urinary excretion of harmine and its metabolites in man and rats
1190	Resorption of drugs from the gastrointestinal tract as predicted by an *in vitro* model
1191	Absorption, distribution, and metabolic fate of psychotropic drugs
1192	Modern view of the absorption, distribution, and elimination of inhalatory anesthetics
1193	Absorption and blood level values for ethosuximide in children and young adults having petit mal or mixed seizure disorders

Table XXXV—Additional References on Pharmacokinetics

Reference	Topic
1204	Pharmacokinetic profile of trimethoprim in man and dog, with the dog absorbing the drug completely
1205	Blood levels of guaiacol glycerol ether mononicotinate in animals, showing a pseudo-first-order absorption by passive transport
1206	Pharmacokinetic aspects of biliary excretion and dose dependence of riboflavin in rat
1207	Pharmacokinetic methods for evaluation of intestinal absorption
1208	Application of Laplace transform for solving differential rate equations in pharmacokinetics
1209	Kinetics of anticoagulant effect of bishydroxycoumarin in man
1210	Relation between drug-elimination kinetics in intact animals and isolated perfused liver systems, using phenylbutazone and bishydroxycoumarin
1211	Review of methods of determining biological half-lives of drugs; comprehensive tabulation of half-lives for many drug substances
1212	Rate of decline of diphenylhydantoin in human plasma
1213	Absorption, blood concentrations, and excretion of pentazocine after oral, intramuscular, and rectal administration in man
1214	Kinetics of glucose transport in isolated dog brain
1215	Absorption, distribution, and excretion of 3-trifluoromethyl-*s*-triazolo(3,4-α)isoquinoline
1216	Kinetics and drug metabolism of sympathomimetic amines in man
1217	Importance of steric, stereochemical, and physicoorganic features in drug metabolism and drug action
1218	Quasilinearization and fitting of nonlinear models of drug metabolism to experimental kinetic data
1219	Pharmacokinetics of urinary excretion of chlorphentermine in man
1220	Pharmacokinetics of dimethylaminophenazone, 4-aminophenazone, and phenazone in rats of various ages
1221	Apparent dose-dependent elimination kinetics as an experimental artifact
1222	Pharmacokinetics of haloperidol, showing the maximum blood level was reached within 15 min. with rapid elimination after subcutaneous administration
1223	Blood and urinary clearance of exogenous serotonin in relation to time and route of administration
1224	Pharmacokinetic and bacteriological properties of new oral cephalosporin compounds
1225	Review of pharmacokinetics and therapeutic importance
1226	Pharmacokinetics of cephalexin
1227	Pharmacodynamics and metabolism of propranolol in man
1228	Pharmacokinetics of trimethoprim in man and animals
1229	Review of pharmacokinetics of chemotherapeutic agents
1230	Kinetics of distribution and metabolism of ataractics of the meprobamate group in mice
1231	Pharmacokinetics of DL-ethyl *trans*-2-dimethylamino-1-phenyl-3-cyclohexene-*trans*-1-carboxylate hydrochloride in man, including blood level and excretion in urine and feces after a single oral dose of tritiated compound
1232	Kinetics of diphenylhydantoin disposition in man
1233	Kinetics of radiohippuran
1234	Kinetics of chloral hydrate metabolism in mice and the effect of ethanol
1235	Kinetics of amylobarbital metabolism in healthy men and women
1236	Kinetics of the anticoagulant effect of heparin

had the same formal dependency on concentration as did erythromycin, with a potency ratio of 6.68:1, erythromycin base to lincomycin base, on a weight basis. The combined effect of erythromycin and lincomycin in Phase I did not antagonize the growth rate of *E. coli* in the subinhibitory range and could be predicted by adding equivalent amounts in accordance with the coincident response–dose curves of erythromycin and lincomycin (Phase I) (1198).

A simple model was proposed and used, in conjunction with an analog computer, to determine the rate constants of buccal absorption of 10 carboxylic acids from solutions of pH 4.0 using a single subject. The rate constants gave a positive correlation with previously determined logarithms of *n*-heptane–0.1 *N* hydrochloric acid partition coefficients (1199).

Monoexponential and biexponential disappearance of drug was observed both from the simulated gut phase of a three-phase *in vitro* model for drug absorption and from the lumen of an *in situ* rat gut. Monoexponential disappearance occurred when accumulation of drug in the membrane phase was low or absent, whereas biexponential disappearance occurred when membrane accumulation was appreciable. In all cases, overall transfer of drug to blood was essentially irreversible. Kinetic analysis of the biexponential lumen-phase data was presented (1200).

Under multiple-dosing conditions at a subcutaneous site, equations were derived which permitted one to estimate the number of doses, *n*, required to approach within $\pm 1\%$ of the asymptotic minimum level. The equations, with numerous term definitions, explained that benzyl alcohol disappears from the subcutaneous cell in an apparent monoexponential manner (1201).

The *in vitro* absorption kinetics for nine drugs were followed, using a perfusion apparatus. Identical perfusion runs were made on everted and noneverted segments of the same rat intestine so that the ratio of directional permeability constants could be calculated. Both negatively and positively charged drug ions exhibited permeability coefficient ratios of around 1.3, while completely unionized drugs showed the expected ratio of 1.0. In light of the similarity in the ratio of permeability constants for drug ions and sodium ions, salicylate was tested in a sodium-free buffer, resulting in a ratio of 1.08. It appeared that the difference in directional permeability constants observed with ionized drugs in the intestine may be explained in relation to sodium transport. It was pointed out that *in vitro* intestinal transport studies could lead to erroneous conclusions concerning the degree of absorption of ionizable drugs *in vivo* (1202).

The urinary excretion rate was studied by administering sulfafurazole under normal physiological conditions and after an alkali load (to eliminate diurnal fluctuations in the urinary pH over a 48-hr. period). The controlled alkaline condition had a marked effect on the urinary excretion of sulfafurazole. The elimination half-life was reduced from a mean 6.3 hr. under normal conditions to a mean 4.4 hr. under alkaline conditions. Similarly, under normal and alkaline conditions, the percentage of drug acetylated was reduced from an average of 34.9% to 25.0%, respectively, and the percentage of total drug excreted increased from a mean 82.7% to 89.9%, respectively (1203).

Additional studies on pharmacokinetics are listed in Table XXXV.

REFERENCES

(1) W. J. McKeehan, *J. Pharm. Sci.*, **52**, 613(1963).
(2) W. J. McKeehan and L. C. Lappas, *ibid.*, **53**, 695(1964).
(3) L. C. Lappas and R. E. Dempski, *ibid.*, **54**, 931(1965).

(4) R. E. Dempski and G. P. Polli, *ibid.*, **55,** 645(1966).
(5) G. P. Polli and L. J. Ravin, *ibid.*, **56,** 781(1967).
(6) L. J. Ravin and P. D. Bernardo, *ibid.*, **57,** 1075(1968).
(7) P. D. Barnardo and E. J. Russo, *ibid.*, **58,** 777(1969).
(8) E. J. Russo and T. L. Benney, *ibid.*, **59,** 883(1970).
(9) S. Oldham, *Mfg. Chem. Aerosol News*, **41,** 43(1970).
(10) A. H. Der Marderosian, *Trans. Symp. Drugs Sea*, **1967,** 19; through *Chem. Abstr.*, **73,** 80428r(1970).
(11) P. R. Burkholder, *ibid.*, **1967,** 87; through *Chem. Abstr.*, **73,** 80429s(1970).
(12) J. Comer, H. Breunig, D. Broadlick, and C. Sampson, *J. Pharm. Sci.*, **59,** 210(1970).
(13) V. Pietra and I. Setnikar, *ibid.*, **59,** 530(1970).
(14) I. Setnikar, *Boll. Chim. Farm.*, **109,** 310(1970); through *Chem. Abstr.*, **73,** 133946s(1970).
(15) M. Miyoshi and K. Kawai, *Kyoto Furitsu Ika Daigaku Zasshi*, **79,** 132(1970); through *Chem. Abstr.*, **73,** 12811k(1970).
(16) W. Fuerst, M. Falk, and H. Lauterbach, *Pharmazie*, **24,** 590(1969); through *Chem. Abstr.*, **72,** 59040c(1970).
(17) R. Wenk and J. Schmid, *Pharm. Prax.*, **8,** 183(1970); through *Chem. Abstr.*, **73,** 123503f(1970).
(18) L. Wurmser and I. Vischniac, *Ann. Pharm. Fr.*, **28,** 377 (1970); through *Chem. Abstr.*, **73,** 133953s(1970).
(19) T. Beritic and D. Dimov, *Lijec. Vjesn.*, **91,** 1208(1969); through *Chem. Abstr.*, **73,** 28800s(1970).
(20) R. Ugarte, *Mex. Farm.*, **33,** 30(1969); through *Chem. Abstr.*, **72,** 24531m(1970).
(21) F. G. Young, *Pharm. Ztg.*, **114,** 1441(1969); through *Chem. Abstr.*, **72,** 24524m(1970).
(22) F. Barr, G. More, and B. Gragg, *J. Pharm. Sci.*, **59,** 262(1970)
(23) H. P. Jaspersen and M. Schlumpf, *Schweiz. Apoth.-Ztg.*, **107,** 560(1969); through *Chem. Abstr.*, **72,** 77369w(1970).
(24) W. Raab and J. Windisch, *Chemotherapy*, **15,** 26(1970); through *Chem. Abstr.*, **72,** 20266f(1970).
(25) K. Thoma, E. Ullmann, and O. Fickel, *Arch. Pharm. (Weinheim)*, **303,** 289(1970); through *Chem. Abstr.*, **73,** 28842g(1970).
(26) *Ibid.*, **303,** 297(1970); through *Chem. Abstr.*, **73,** 28843h (1970).
(27) N. K. Patel, *Can. J. Pharm. Sci.*, **2,** 97(1967); through *Chem. Abstr.*, **72,** 103677s(1970).
(28) N. K. Patel and J. M. Romanowski, *J. Pharm. Sci.*, **59,** 372(1970).
(29) V. Ecker and E. Fischer, *Harokeach Haivri*, **13,** 350(1969); through *Chem. Abstr.*, **72,** 93314e(1970).
(30) J. Vasani and R. E. King, *Amer. J. Pharm.*, **141,** 177(1969); through *Chem. Abstr.*, **72,** 93312c(1970).
(31) H. Ansel and G. Cabre, *J. Pharm. Sci.*, **59,** 478(1970).
(32) N. Tufegdzic and S. Mirkovic, *Acta Pharm. Jugoslav.*, **18,** 219(1968); through *Chem. Abstr.*, **73,** 69795n(1970).
(33) W. Salt and D. Wiseman, *J. Pharm. Pharmacol.*, **22,** 261(1970).
(34) L. A. Ivanova and T. S. Kondrat'eva, *Farmatsiya*, **19,** 23(1970); through *Chem. Abstr.*, **73,** 7184d(1970).
(35) L. Lachman, *Bull. Parenteral Drug Ass.*, **22,** 127(1968); through *Chem. Abstr.*, **73,** 69743u(1970).
(36) A. Russel, J. Jenkins, and I. H. Harrison, *Advan. Appl. Microbiol.*, **9,** 1(1967); through *Chem. Abstr.*, **72,** 82917c(1970).
(37) S. P. Eriksen, *Drug Cosmet. Ind.*, **107,** 36(1970).
(38) R. Kvamme, *Norg. Apotekerforen. Tidsskr.*, **77,** 468(1969); through *Chem. Abstr.*, **73,** 7148v(1970).
(39) T. McCarthy, *J. Mond. Pharm.*, **12,** 321(1969); through *Chem. Abstr.*, **73,** 69791h(1970).
(40) M. Van Ooteghem and H. Herbots, *Pharm. Acta Helv.*, **44,** 602(1969); through *Chem. Abstr.*, **72,** 24561w(1970).
(41) L. Worthen and H. Bond, *J. Pharm. Sci.*, **59,** 1185(1970).
(42) H. Laycock and B. Mulley, *J. Pharm. Pharmacol.*, **22,** 157S(1970).
(43) P. Z. Bedoukian, *Amer. Perfum. Cosmet.*, **85,** 25(1970).
(44) L. Appell, *ibid.*, **85,** 49(1970).
(45) J. E. Amoore, *J. Soc. Cosmet. Chem.*, **21,** 99(1970).
(46) H. Nursten, *Flavour Ind.*, **1,** 521(1970); through *Chem. Abstr.*, **73,** 80393a(1970).
(47) P. Bedoukian, *Amer. Perfum. Cosmet.*, **85,** 35(1970).
(48) T. Sato and K. Sudo, *Nippon Daikaku Yakugaku Kenkyu Hokoku*, **10,** 13(1969); through *Chem. Abstr.*, **73,** 59208j(1970).
(49) M. Blanco, S. Eriksen, and M. Boghosian, *Drug. Cosmet. Ind.*, **107,** 44(1970).
(50) D. Davies, B. Meakin, and S. Moss, *J. Pharm. Pharmacol.*, **22,** 43S(1970).
(51) E. Pandula and E. Farkas, *Acta Pharm. Hung.*, **40,** 165 (1970); through *Chem. Abstr.*, **73,** 91210q(1970).
(52) P. Gantes, J. Barat, and H. Joly, *Ann. Pharm. Fr.*, **27,** 645(1969); through *Chem. Abstr.*, **72,** 136350h(1970).
(53) J. G. Half, *Dan. Tiksskr. Farm.*, **43,** 156(1969); through *Chem. Abstr.*, **72,** 15719b(1970).
(54) P. Lundgren and L. Landersjo, *Acta Pharm. Suecica*, **7,** 133(1970); through *Chem. Abstr.*, **73,** 28848p(1970).
(55) N. Tuchel, *Farmacia*, **17,** 281(1969); through *Chem. Abstr.*, **72,** 24550s(1970).
(56) *Ibid.*, **17,** 337(1969); through *Chem. Abstr.*, **72,** 24551t (1970).
(57) F. Botari, M. Mannelli, and M. F. Saettone, *J. Pharm. Sci.*, **59,** 1663(1970).
(58) J. Burianek and J. Cifka, *J. Label. Compounds*, **6,** 224 (1970); through *Chem. Abstr.*, **73,** 112904m(1970).
(59) Z. Rybakow and J. Cifka, *ibid.*, **6,** 240(1970); through *Chem. Abstr.*, **73,** 101991m(1970).
(60) E. Bjerkelund, F. Gram, and T. Waaler, *Pharm. Acta Helv.*, **44,** 745(1969); through *Chem. Abstr.*, **72,** 59023z(1970).
(61) F. Jaminet, L. Delattre, J. P. Delporte, and A. Moes, *ibid.*, **45,** 60(1970); through *Chem. Abstr.*, **72,** 59031a(1970).
(62) P. Buri, C. Meyer, and P. Vuagna, *ibid.*, **44,** 764(1969); through *Chem. Abstr.*, **72,** 35748p(1970).
(63) K. C. Guven and A. Aras, *Eczacilik Bul.*, **12,** 72(1970); through *Chem. Abstr.*, **73,** 102001a(1970).
(64) G. Vaisman and R. Shpak, *Farm. Zh.*, **24,** 54(1969); through *Chem. Abstr.*, **72,** 24580b(1970).
(65) E. Kalatzis, *J. Pharm. Sci.*, **59,** 193(1970).
(66) W. Ritschel and G. Ritschel-Beurlin, *Praep. Pharm.*, **6,** 21(1970); through *Chem. Abstr.*, **72,** 136347n(1970).
(67) M. Horioka, M. Tsuruoka, and Y. Shinmura, *Kyushu Yakugakkai Kaioh*, **23,** 31(1969); through *Chem. Abstr.*, **72,** 93307e (1970).
(68) A. Kamishiro, T. Isobe, Y. Ueda, M. Kanda, H. Kamimura, and M. Hosoi, *ibid.*, **23,** 27(1969); through *Chem. Abstr.*, **72,** 93322f(1970).
(69) K. Satake and M. Hosoi, *ibid.*, **23,** 21(1969); through *Chem. Abstr.*, **72,** 93325j(1970).
(70) H. Nogami, J. Hasegawa, and M. Iwatsuru, *Chem. Pharm. Bull.*, **18,** 2297(1970).
(71) C. Kelly, *J. Pharm. Sci.*, **59,** 1053(1970).
(72) M. Haavisto and V. Krogerus, *Farm. Aikak.*, **78,** 131(1969); through *Chem. Abstr.*, **72,** 136343h(1970).
(73) H. Staudinger, E. Degkwitz, and V. Ullrich, *Med. Welt*, **51,** 2747(1969); through *Chem. Abstr.*, **72,** 24526p(1970).
(74) D. L. Simmons, H. S. L. Woo, J. J. Liston, and R. J. Ranz, *Can. J. Pharm. Sci.*, **2,** 101(1967); through *Chem. Abstr.*, **72,** 103678t(1970).
(75) V. Torrado and J. Juan, *An. Real Acad. Farm.*, **35,** 375 (1969); through *Chem. Abstr.*, **72,** 103674p(1970).
(76) K. James and R. Leach, *J. Pharm. Pharmacol.*, **22,** 607 (1970).
(77) M. Sarsunova, L. Kraus, J. Ludva, M. Krausova, and V. Schwarz, *Cesk. Farm.*, **18,** 445(1969); through *Chem. Abstr.*, **72,** 125034g(1970).
(78) A. Rasmussen, *Arch. Pharm. Chemi*, **77,** 164(1970); through *Chem. Abstr.*, **73,** 18463v(1970).
(79) P. Gladyshev and M. Goryaev, *Izv. Akad. Nauk Kaz. SSR, Ser. Khim.* **19,** 85(1969); through *Chem. Abstr.*, **72,** 24566b (1970).
(80) A. Chodakowski, *Farm. Pol.*, **25,** 529(1969); through *Chem. Abstr.*, **72,** 24522j(1970).
(81) M. Liska and M. Zahradnicek, *Cesk. Farm.*, **18,** 380(1969); through *Chem. Abstr.*, **72,** 93303a(1970).
(82) *Ibid.*, **18,** 438(1969); through *Chem. Abstr.*, **72,** 125030c (1970).
(83) K. Matsushima and K. Kiyota, *Iryo*, **23,** 1561(1969); through *Chem. Abstr.*, **73,** 112897m(1970).
(84) G. Schenck, *Asian Med. J.*, **13,** 149(1970); through *Chem. Abstr.*, **73,** 123448s(1970).
(85) J. Portych, M. Chalabala, and H. Bazantova, *Cesk. Farm.*, **18,** 258(1969); through *Chem. Abstr.*, **72,** 24562x(1970).

(86) E. Minkov, R. Nacheva, and L. Nedeleva, *Pharmazie*, **24,** 770(1969); through *Chem. Abstr.*, **72,** 125033f(1970).

(87) S. L. Lin, *Bull. Parenteral Drug Ass.*, **24,** 83(1970); through *Chem. Abstr.*, **73,** 59260v(1970).

(88) S. Larsen and V. Jensen, *Dan. Tidsskr. Farm.*, **44,** 21(1970); through *Chem. Abstr.*, **72,** 136349q(1970).

(89) A. Foster, *Australas. J. Pharm.*, **50,** S86(1969); through *Chem. Abstr.*, **72,** 136346m(1970).

(90) M. Havlova, M. Nobilis, and L. Patocka, *Cesk. Farm.*, **18,** 390(1969); through *Chem. Abstr.*, **72,** 93304b(1970).

(91) V. Kalis and E. Kirillova, *Latv. PSR Ziant. Akad. Vestis, Kim. Ser.*, **1,** 29(1970); through *Chem. Abstr.*, **72,** 125029j(1970).

(92) O. Ryaposova and B. Nazarov, *Farmatisya (Moscow)*, **19,** 21(1970); through *Chem. Abstr.*, **73,** 80445u(1970).

(93) R. Painter and J. Minta, *Vox Sang.*, **17,** 434(1969); through *Chem. Abstr.*, **72,** 24560v(1970).

(94) H. Delonica, A. Puech, G. Segura, and J. Youakim, *J. Pharm. Belg.*, **24,** 317(1969); through *Chem. Abstr.*, **72,** 35755p (1970).

(95) H. Marquardt, *Fr. Pharm.*, **23,** 13(1970); through *Chem. Abstr.*, **73,** 28890w(1970).

(96) T. N. Calvey, *J. Pharm. Pharmacol.*, **22,** 533(1970).

(97) Z. Olszewski, L. Wendt, H. Bujar, and B. Skurska-Jagielka, *Farm. Pol.*, **25,** 507(1969); through *Chem. Abstr.*, **72,** 35746m(1970).

(98) J. Carstensen, *J. Pharm. Sci.*, **59,** 1140(1970).

(99) N. F. H. Ho and J. A. Goeman, *Drug Intel. Clin. Pharm.*, **4,** 69(1970); through *Chem. Abstr.*, **73,** 7159z(1970).

(100) K. S. Lin, *Bull. Parenteral Drug Ass.*, **22,** 299(1968); through *Chem. Abstr.*, **73,** 59268d(1970).

(101) C. J. Lintner, J. I. Northam, and R. J. Cole, *Amer. Perfum. Cosmet.*, **85,** 31(1970).

(102) H. V. Maulding and M. A. Zoglio, *J. Pharm. Sci.*, **59,** 333(1970).

(103) D. Bentley, *ibid.*, **59,** 464(1970).

(104) E. Pawelczyk and T. Hermann, *Diss. Pharm. Pharmacol.*, **21,** 267(1969); through *Chem. Abstr.*, **62,** 15718a(1970).

(105) E. Pawelczyk, T. Hermann, and K. Jurkiewicz, *ibid.*, **22,** 153(1970); through *Chem. Abstr.*, **73,** 112906p(1970).

(106) E. Pawelczyk, M. Zajac, and M. Downar, *ibid.*, **21,** 475 (1969); through *Chem. Abstr.*, **72,** 35731c(1970).

(107) E. Pawelczyk, T. Hermann, and R. Sukowski, *ibid.*, **21,** 481(1969); through *Chem. Abstr.*, **72,** 35729h(1970).

(108) E. Pawelczyk and R. Wachowiak, *Acta Pol. Pharm.*, **26,** 433(1969); through *Chem. Abstr.*, **72,** 136355p(1970).

(109) E. Pawelczyk and M. Zajac, *ibid.*, **27,** 113(1970); through *Chem. Abstr.*, **73,** 80440p(1970).

(110) E. Pawelczyk and R. Wachowiak, *Diss. Pharm. Pharmacol.*, **21,** 491(1969); through *Chem. Abstr.*, **72,** 35730b(1970).

(111) E. Pawelczyk, R. Wachowiak, and I. Pluta, *ibid.*, **22,** 165(1970); through *Chem. Abstr.*, **73,** 102000z(1970).

(112) R. Adamski and K. Pawelczyk, *Farm. Pol.*, **25,** 979(1969); through *Chem. Abstr.*, **73,** 38494j(1970).

(113) *Ibid.*, **25,** 1049(1969); through *Chem. Abstr.*, **73,** 28841f (1970).

(114) *Ibid.*, **26,** 51(1970); through *Chem. Abstr.*, **73,** 59266b (1970).

(115) S. Naito and K. Fukui, *Chem. Pharm. Bull.*, **18,** 820(1970).

(116) S. Naito and S. Bessho, *ibid.*, **18,** 651(1970).

(117) H. Nogami, K. Kigasawa, N. Ikari, H. Ohtani, and M. Takeyama, *Yakugaku Zasshi*, **90,** 967(1970).

(118) H. Nogami, K. Kigasawa, N. Ikari, K. Nakamura, and H. Ohtani, *ibid.*, **90,** 973(1970).

(119) H. Nogami, K. Kigasawa, N. Ikari, K. Nakamura, H. Ohtani, K. Takeuchi, and S. Haga, *ibid.*, **90,** 979(1970).

(120) R. Washkuhn, S. Reutrakul, and J. Robinson, *J. Pharm. Sci.*, **59,** 779(1970).

(121) K. Murthy and E. Rippie, *ibid.*, **59,** 459(1970).

(122) E. Rattie, E. Shami, L. Dittert, and J. Swintosky, *ibid.*, **59,** 1738(1970).

(123) S. L. Hem, E. J. Russo, R. J. Harwood, B. H. Tejani, S. M. Bahal, and R. S. Levi, *ibid.*, **59,** 376(1970).

(124) T. O. Oesterling and J. H. Gustafson, *ibid.*, **59,** 1612(1970).

(125) G. Flynn and D. J. Lamb, *ibid.*, **59,** 1433(1970).

(126) R. E. Notari, M. L. Chin, and A. Cardoni, *ibid.*, **59,** 28(1970).

(127) P.-H. Chung, T.-F., Chin, and J. L. Lach, *ibid.*, **59,** 1300(1970).

(128) H. A. M. El-Shibini, A. M. Saleh, and M. M. Motwai, *Pharmazie*, **24,** 687(1969); through *Chem. Abstr.*, **72,** 93308f(1970).

(129) A. Saleh, H. El-Shibini, and M. M. Motawi, *ibid.*, **24,** 757(1969); through *Chem. Abstr.*, **72,** 125028h(1970).

(130) S. S. Kornblum, *Drug Cosmet. Ind.*, **106,** 42(1970).

(131) K. Shirahama, S. Kawamura, and R. Matuura, *Mem. Fac. Sci. Kyushu Univ., Ser. C*, **7,** 11(1970); through *Chem. Abstr.*, **73,** 123476z(1970).

(132) I. Grabowska, *Acta Pol. Pharm.*, **27,** 23(1970); through *Chem. Abstr.*, **73,** 80442r(1970).

(133) A. K. Ray and M. N. Das, *J. Chem. Soc. (A)*, **1970,** 464.

(134) P. Speiser, *J. Pharm. Belg.*, **24,** 492(1969); through *Chem. Abstr.*, **72,** 136360m(1970).

(135) E. Davey and J. Murray, *Pharm. J.*, **203,** 737(1969); through *Chem. Abstr.*, **72,** 136356q(1970).

(136) B. M. Colombo and P. Causa, *Farmaco, Ed. Prat.*, **25,** 95(1970); through *Chem. Abstr.*, **72,** 103673n(1970).

(137) C. R. Weber and V. Das Gupta, *J. Hosp. Pharm.*, **28,** 200(1970); through *Chem. Abstr.*, **73,** 112907q(1970).

(138) M. Sterescu, R. Motocescu, and E. Mihalas, *Farmacia (Bucharest)*, **18,** 429(1970); through *Chem. Abstr.*, **73,** 133962u(1970).

(139) J. A. Wesselingh and A. Van't Hogg, *Trans. Inst. Chem. Eng.*, **48,** T69(1970); through *Chem. Abstr.*, **73,** 38892n(1970).

(140) T. O. Oesterling, *J. Pharm. Sci.*, **59,** 63(1970).

(141) T. O. Oesterling and E. L. Rowe, *ibid.*, **59,** 175(1970).

(142) B. M. Trivedi and R. K. Patel, *Hindustan Antibiot. Bull.*, **12,** 131(1970); through *Chem. Abstr.*, **73,** 112921q(1970).

(143) J. Jacobs, I. Nathan, E. Superstine, and T. Sacks, *Drug Intel. Clin. Pharm.*, **4,** 204(1970); through *Chem. Abstr.*, **73,** 101996s (1970).

(144) Y. Akagi and T. Yashiki, *Takeda Kenkyusho Ho*, **29,** 102 (1970); through *Chem. Abstr.*, **73,** 80441q(1970).

(145) H. Hsu and S. Yao, *Tai-Wan Yao Hsueh Tsa Chih*, **18,** 56(1966); through *Chem. Abstr.*, **72,** 136377x(1970).

(146) M. A. Kassem, A. Sina, and M. K. Youssef, *Pharm. Ztg.*, **115,** 1036(1970); through *Chem. Abstr.*, **73,** 101993p(1970).

(147) P. Reusser, *Fresenius' Z. Anal. Chem.*, **248,** 317(1969); through *Chem. Abstr.*, **72,** 136315a(1970).

(148) A. P. Kondrat'eva, G. S. Libinson, and B. P. Bruns, *Antibiotiki*, **15,** 722(1970); through *Chem. Abstr.*, **73,** 101994q(1970).

(149) F. Said, M. M. Amer, and K. N. Girgis, *Bull. Fac. Pharm., Cairo Univ.*, **8,** 31(1969); through *Chem. Abstr.*, **73,** 38497n(1970).

(150) M. Khristov, S. Againa, and P. Isov, *Farmatsiya (Sofia)*, **20,** 31(1970); through *Chem. Abstr.*, **73,** 38499q(1970).

(151) M. Khristov, M. Loseva, and D. Iovchev, *ibid.*, **19,** 29 (1969); through *Chem. Abstr.*, **72,** 35736h(1970).

(152) M. Heward, D. A. Norton, and S. M. Rivers, *Pharm. J.*, **204,** 386(1970).

(153) A. I. Kas'yan, *Antibiotiki*, **4,** 32(1969); through *Chem. Abstr.*, **72,** 93306d(1970).

(154) S. Burdarov, D. Mitev, and S. Againa, *Farmatsiya*, **20,** 32(1970); through *Chem. Abstr.*, **73,** 112908r(1970).

(155) R. Thorpe, R. Stretton, and J. Watson-Walker, *Loughborough Univ. Technol., Dep. Chem., Sum. Final Year Stud. Proj. Theses*, **10,** 64(1969); through *Chem. Abstr.*, **73,** 28840e(1970).

(156) J. Oxley and R. Stretton, *ibid.*, **10,** 48(1969); through *Chem. Abstr.*, **73,** 28839m(1970).

(157) A. Gill, R. Severson, and N. Ho, *Drug Intel. Clin. Pharm.*, **4,** 243(1970); through *Chem. Abstr.*, **73,** 133943p(1970).

(158) F. Saccani, *Boll. Chim. Farm.*, **109,** 1(1970); through *Chem. Abstr.*, **73,** 28799y(1970).

(159) A. J. Forlano, C. I. Jarowski, H. F. Hammer, and E. G. Merritt, *J. Pharm. Sci.*, **59,** 121(1970).

(160) T. Ammo, M. Washitake, Y. Takashima, and S. Sato, *Bitamin*, **40,** 325(1969); through *Chem. Abstr.*, **72,** 47326m(1970).

(161) R. Adamski and R. Dobrucki, *Farm. Pol.*, **25,** 415(1969); through *Chem. Abstr.*, **72,** 6221f(1970).

(162) *Ibid.*, **25,** 535(1969); through *Chem. Abstr.*, **72,** 24555x (1970).

(163) H. Leszczynska Bakal and H. Siedlanowska Krowczynska, *Cesk. Farm.*, **19,** 109(1970); through *Chem. Abstr.*, **73,** 59265a (1970).

(164) S. Bhattacharya, *J. Inst. Chem., Calcutta*, **41,** 263(1969); through *Chem. Abstr.*, **72,** 136354n(1970).

(165) *Ibid.*, **42,** 9(1970); through *Chem. Abstr.*, **73,** 28831c(1970).

(166) *Ibid.*, **42,** 75(1970); through *Chem. Abstr.*, **73,** 38504m (1970).
(167) F. Said, M. M. Amer, and K. Girgis, *Bull. Fac. Pharm., Cairo Univ.*, **8,** 21(1969); through *Chem. Abstr.*, **73,** 38496m(1970).
(168) J. Boissier and J. Tillement, *Ann. Pharm. Fr.*, **27,** 743 (1969); through *Chem. Abstr.*, **73,** 38506q(1970).
(169) F. Said, M. M. Amer, and K. Girgis, *Bull. Fac. Pharm., Cairo Univ.*, **8,** 11(1969); through *Chem. Abstr.*, **73,** 38495k(1970).
(170) G. Ceschel and F. Fontani, *Boll. Chim. Farm.*, **108,** 449 (1969); through *Chem. Abstr.*, **72,** 24556y(1970).
(171) C. Bertellini, *ibid.*, **109,** 111(1970); through *Chem. Abstr.*, **73,** 38505p(1970).
(172) C. T. Shin, B. J. Sciarrone, and C. A. Discher, *J. Pharm. Sci.*, **59,** 297(1970).
(173) K. Guven and S. Kanber, *Eczacilik Bul.*, **11,** 161(1969); through *Chem. Abstr.*, **72,** 70609r(1970).
(174) *Ibid.*, **11,** 185(1969); through *Chem. Abstr.*, **73,** 7179f (1970).
(175) M. Ohmae and G. Katsui, *Bitamin*, **41,** 173(1970); through *Chem. Abstr.*, **73,** 28835g(1970).
(176) *Ibid.*, **41,** 178(1970); through *Chem. Abstr.*, **73,** 28834f (1970).
(177) N. Daabis and F. El-Khawas, *Pharmazie*, **24,** 750(1969); through *Chem. Abstr.*, **72,** 125027g(1970).
(178) P. Ban, *Farmacia (Bucharest)*, **18,** 1(1970); through *Chem. Abstr.*, **73,** 80422j(1970).
(179) R. Barry and M. Weiss, *J. Amer. Pharm. Ass.*, **NS10,** 601(1970).
(180) H. Valfre, *Rev. Quim. Ind.*, **39,** 14(1970); through *Chem. Abstr.*, **73,** 59219p(1970).
(181) A. A. Kassem, N. Rofael, K. A. El Soud, and A. Montasser, *Bull. Fac. Pharm., Cairo Univ.*, **8,** 223(1969); through *Chem. Abstr.*, **73,** 38517u(1970).
(182) R. Huettenrauch, *Pharmazie*, **24,** 761(1969); through *Chem. Abstr.*, **72,** 125014a(1970).
(183) A. Hussein, A. A. Kassem, and W. Darwish, *Bull. Fac. Pharm., Cairo Univ.*, **8,** 213(1969); through *Chem. Abstr.*, **73,** 38503m(1970).
(184) J. R. Boissier and J. P. Tillement, *Ann. Pharm. Fr.*, **27,** 599(1969); through *Chem. Abstr.*, **72,** 12503j(1970).
(185) K. C. Agarwal and D. Agarwal, *Indian J. Technol.*, **7,** 410(1969); through *Chem. Abstr.*, **72,** 70602h(1970).
(186) F. Banci, P. Del Grande, and A. Monai, *Arzneim.-Forsch.*, **20,** 1030(1970); through *Chem. Abstr.*, **73,** 133958x(1970).
(187) K. Guven and S. Kanber, *Eczacilik Bul.*, **11,** 170(1969); through *Chem. Abstr.*, **72,** 70603j(1970).
(188) L. Rafinski, T. Przadka, and B. Szczeniewska, *Farm. Pol.*, **25,** 541(1969); through *Chem. Abstr.*, **72,** 24557z(1970).
(189) L. Luzzi, *J. Pharm. Sci.*, **59,** 1367(1970).
(190) H. Nack, *J. Soc. Cosmet. Chem.*, **21,** 85(1970).
(191) O. Jungersen, *Dan. Tidsskr. Farm.*, **44,** 98(1970); through *Chem. Abstr.*, **73,** 112873a(1970).
(192) H. Naumann, *Pharm. Prax.*, **1970,** 153; through *Chem. Abstr.*, **73,** 101958f(1970).
(193) B. S. Kovacs, *Gyogyszereszet*, **13,** 333(1969); through *Chem. Abstr.*, **72,** 15694q(1970).
(194) H. Burger, *Pharm. Weekbl.*, **105,** 905(1970); through *Chem. Abstr.*, **73,** 101959g(1970).
(195) S. Larsen, *Dan. Tidsskr. Farm.*, **43,** 238(1969); through *Chem. Abstr.*, **72,** 136307z(1970).
(196) N. Pilpek, *Mfg. Chem. Aerosol News*, **41,** 19(1970).
(197) R. Tawashi, *Drug Cosmet. Ind.*, **106,** 46(1970).
(198) T. M. Jones, *J. Soc. Cosmet. Chem.*, **21,** 483(1970).
(199) K. Dziegielewski, I. Koller, E. Zukowski, D. Ruczaj, K. Smereczynski, and J. Karasinska, *Przem. Chem.*, **149,** 161(1970); through *Chem. Abstr.*, **73,** 28876w(1970).
(200) P. A. Van Damme, *Pharm. Acta Helv.*, **45,** 564(1970); through *Chem. Abstr.*, **73,** 91215v(1970).
(201) V. Yanchick and G. Sperandio, *Bull. Parenteral Drug Ass.*, **23,** 53(1969); through *Chem. Abstr.*, **73,** 38524u(1970).
(202) W. Kramer, J. J. Tanja, and W. L. Harrison, *Amer. J. Hosp. Pharm.*, **27,** 548(1970).
(203) N. M. Davis, S. Turco, and E. Sivelly, *ibid.*, **27,** 822(1970).
(204) K. T. Johnson, C. D. Hepler, and J. P. B. Gallardo, *ibid.*, **27,** 968(1970).
(205) C. W. Ogle and Y. T. Ng, *Singapore Med. J.*, **10,** 127 (1969); through *Chem. Abstr.*, **72,** 47331k(1970).
(206) R. W. Anderson and C. J. Latiolais, *Amer. J. Hosp. Pharm.*, **27,** 540(1970).
(207) P. Lundgren and L. Landersjo, *Acta Pharm. Suecica*, **7,** 407(1970); through *Chem. Abstr.*, **73,** 133960s(1970).
(208) L. Colombetti, D. Goodwin, and R. Hinkley, *J. Nucl. Med.*, **10,** 633(1969); through *Chem. Abstr.*, **72,** 35770q(1970).
(209) C. De Sanctis and G. Maffei, *Minerva Med.*, **60,** 3889 (1969); through *Chem. Abstr.*, **72,** 93305c(1970).
(210) E. Pandula, E. Farkas, and A. Nagykaldi, *Pharmazie*, **25,** 254(1970); through *Chem. Abstr.*, **73,** 102005e(1970).
(211) A. Somogyi and K. Kovacs, *Cancer Res.*, **30,** 1958(1970); through *Chem. Abstr.*, **73,** 69800k(1970).
(212) S. Ljungberg and R. Jeppsson, *Acta Pharm. Suecica*, **7,** 435(1970); through *Chem. Abstr.*, **73,** 118712u(1970).
(213) J. Kulcsar-Gergely, *Acta Pharm. Hung.*, **40,** 97(1970); through *Chem. Abstr.*, **73,** 48524h(1970).
(214) B. M. Colombo, P. Primavera, and D. Lojodice, *Farmaco, Ed. Prat.*, **25,** 241(1970); through *Chem. Abstr.*, **73,** 7180z(1970).
(215) A. Hussein, A. Kassem, and M. El-Samaligy, *Bull. Fac. Pharm., Cairo Univ.*, **7,** 155(1968); through *Chem. Abstr.*, **73,** 38498p(1970).
(216) I. R. Gnidets, *Farm. Zh. (Kiev)*, **24,** 70(1969); through *Chem. Abstr.*, **72,** 59029f(1970).
(217) M. Kassem, A. Kassem, and H. Ammar, *Pharm. Acta Helv.*, **44,** 611(1969); through *Chem. Abstr.*, **72,** 24553v(1970).
(218) *Ibid.*, **44,** 667(1969); through *Chem. Abstr.*, **72,** 6220e (1970).
(219) A. Kassem, N. Rofael, S. Amin, and L. Soliman, *Bull. Fac. Pharm., Cairo Univ.*, **7,** 47(1968); through *Chem. Abstr.*, **73,** 38516t(1970).
(220) A. Kassem and N. Rofael, *ibid.*, **8,** 169(1969); through *Chem. Abstr.*, **73,** 38515s(1970).
(221) W. Horsch and H. Kuehn, *Pharmazie*, **24,** 549(1969); through *Chem. Abstr.*, **72,** 24558a(1970).
(222) J. Jacobs, *Pharm. J.*, **205,** 437(1970).
(223) H. Vranckx, G. Lambert, and M. Roland, *J. Pharm. Belg.*, **25,** 115(1970); through *Chem. Abstr.*, **73,** 59230k(1970).
(224) L. Cavatorta, E. Pietra, and R. Allievi, *Boll. Chim. Farm.*, **108,** 488(1969); through *Chem. Abstr.*, **72,** 35749q(1970).
(225) D. F. Cooper and C. W. Barrett, *Pharm. J.*, **205,** 186(1970).
(226) I. N. Kurchenko, *Farmatsiya*, **19,** 20(1970); through *Chem. Abstr.*, **73,** 7178e(1970).
(227) L. Blecher and L. Burnette, *Bull. Parenteral Drug Ass.*, **23,** 124(1969); through *Chem. Abstr.*, **73,** 69746x(1970).
(228) Z. Gold, *Farm. Pol.*, **25,** 661(1969); through *Chem. Abstr.*, **72,** 70601g(1970).
(229) J. Davignon, *Bull. Parenteral Drug Ass.*, **23,** 83(1969); through *Chem. Abstr.*, **73,** 69798r(1970).
(230) R. Alasheeva and N. Kudakova, *Farmatsiya*, **18,** 61 (1969); through *Chem. Abstr.*, **72,** 24579h(1970).
(231) K. Nakano, *Iryo*, **23,** 1441(1969); through *Chem. Abstr.*, **72,** 136348p(1970).
(232) N. Bugrim and E. Zatula, *Farmatsiya*, **18,** 66(1969); through *Chem. Abstr.*, **72,** 24578g(1970).
(233) H. Irmscher and J. Saeckel, *Pharm. Prax.*, **8,** 186(1970); through *Chem. Abstr.*, **73,** 123485b(1970).
(234) E. Sandell, *Acta Pharm. Suecica*, **6,** 637(1969); through *Chem. Abstr.*, **72,** 103689x(1970).
(235) G. Crivellaro, *Farmaco, Ed. Prat.*, **25,** 277(1970); through *Chem. Abstr.*, **73,** 38453v(1970).
(236) P. Frauch, *Pharm. Acta Helv.*, **45,** 329(1970); through *Chem. Abstr.*, **73,** 38521r(1970).
(237) D. Peacock and K. Ridgway, *J. Pharm. Pharmacol.*, **22,** 131S(1970).
(238) K. Rasmussen and V. Jensen, *Dan. Tidsskr. Farm.*, **43,** 160(1969); through *Chem. Abstr.*, **72,** 24571z(1970).
(239) D. A. Gunther, *Amer. Perfum. Cosmet.*, **85,** 35(1970).
(240) W. Guess, *Bull. Parenteral Drug. Ass.*, **24,** 68(1970); through *Chem. Abstr.*, **73,** 38448x(1970).
(241) B. Joyner, *Labo-Pharma-Probl. Tech.*, **180,** 71(1969); through *Chem. Abstr.*, **72,** 136362p(1970).
(242) Y. Y. Chen, *J. Pharm. Sci.*, **59,** 717(1970).
(243) J. Myers, *Chem. Drug.*, **192,** 232(1969); through *Chem. Abstr.*, **72,** 24572a(1970).
(244) H. Weiss, *Pharm. Zentralh.*, **108,** 747(1969); through *Chem. Abstr.*, **72,** 35740e(1970).

(245) G. Hangay, *Magy. Kem. Lapja*, **24,** 505(1969); through *Chem. Abstr.*, **72,** 93296a(1970).
(246) W. Kuehn, *Kerntechnik*, **11,** 523(1969); through *Chem. Abstr.*, **72,** 15695r(1970).
(247) R. Huettenrauch, *Pharmazie*, **25,** 270(1970); through *Chem. Abstr.*, **73,** 102006f(1970).
(248) M. P. Calhoun, M. White, and F. W. Bowman, *J. Pharm. Sci.*, **59,** 1022(1970).
(249) W. Wendland and K. Kowalke, *Pharmazie*, **24,** 691(1969); through *Chem. Abstr.*, **72,** 59024a(1970).
(250) J. Hartvich, *Cesk. Farm.*, **19,** 147(1970); through *Chem. Abstr.*, **73,** 80414h(1970).
(251) J. Dos Santos, *Rev. Port. Farm.*, **20,** 8(1970); through *Chem. Abstr.*, **73,** 133941m(1970).
(252) M. Nekola, *Pharm. Ind.*, **32,** 371(1970); through *Chem. Abstr.*, **73,** 69748z(1970).
(253) A. W. Michalson, *Amer. Perfum. Cosmet.*, **85,** 37(1970).
(254) N. Stoichev, *Pharm. Ind.*, **31,** 953(1969); through *Chem. Abstr.*, **72,** 103680n(1970).
(255) J. L. Livingstone, *Mfg. Chem. Aerosol News*, **41,** 23(1970).
(256) D. E. Fonner, Jr., J. R. Buck, and G. S. Banker, *J. Pharm. Sci.*, **59,** 1587(1970).
(257) D. F. Kelsall, K. J. Reid, and C. J. Restarick, *Powder Technol.*, **3,** 170(1970).
(258) B. Dodson, *ibid.*, **3,** 213(1970).
(259) T. G. Owe Berg and L. E. Avis, *ibid.*, **4,** 27(1970).
(260) F. A. Dullien, E. Rhodes, and S. R. Schroeter, *ibid.*, **3,** 124(1970).
(261) J. S. Hirschhorn, *ibid.*, **4,** 1(1970).
(262) J. R. F. Arthur, *ibid.*, **3,** 195(1970).
(263) A. Otsuka, H. Sunada, K. Danjo, and M. Makagaki, *Yakugaku Zasshi*, **90,** 244(1970).
(264) J. J. Kelly, *J. Soc. Cosmet. Chem.*, **21,** 37(1970).
(265) P. J. Lloyd, P. C. M. Yeung, and D. C. Freshwater, *ibid.*, **21,** 205(1970).
(266) J. C. Williams, *Powder Technol.*, **3,** 189(1970).
(267) J. C. Williams and M. A. Rahman, *J. Soc. Cosmet. Chem.*, **21,** 3(1970).
(268) J. Okada, K. Hozumi, Y. Matsuda, and F. Yoshinobu, *Yakugaku Zasshi*, **90,** 1532(1970).
(269) Y. Miyake, C. Sadakata, K. Tatsuishi, and S. Toyoshima, *ibid.*, **90,** 1107(1970).
(270) G. Irwin, G. Dodson, and L. Ravin, *J. Pharm. Sci.*, **59,** 547(1970).
(271) J. Mitsui, *Chem. Pharm. Bull.*, **18,** 1535(1970).
(272) J. Mitsui, R. Aoyama, and S. Kaga, *ibid.*, **18,** 1541(1970).
(273) K. Ridgway and J. Scotton, *J. Pharm. Pharmacol.*, **22,** 24S(1970).
(274) H. Kristensen and V. Jensen, *Dan. Tidsskr. Farm.*, **43,** 205(1969); through *Chem. Abstr.*, **72,** 70605m(1970).
(275) H. Kristensen, *ibid.*, **43,** 213(1969); through *Chem. Abstr.*, **72,** 70606n(1970).
(276) D. Hanssen, C. Fuehrer, and B. Schaefer, *Pharm. Ind.*, **32,** 97(1970); through *Chem. Abstr.*, **73,** 18469b(1970).
(277) S. Ogawa, M. Hirayama, and H. Nakajima, *Zairyo*, **19,** 565(1970); through *Chem. Abstr.*, **73,** 69816v(1970).
(278) R. Huettenrauch, *Pharmazie*, **24,** 626(1969); through *Chem. Abstr.*, **72,** 59037g(1970).
(279) P. Fuchs, E. Schottky, and G. Schenck, *Pharm. Ind.*, **32,** 581(1970); through *Chem. Abstr.*, **73,** 102014g(1970).
(280) P. Fuchs, E. Schottky, and G. Schenck, *ibid.*, **32,** 390 (1970); through *Chem. Abstr.*, **73,** 80458a(1970).
(281) D. Duchene, A. Djiane, and F. Puisieuz, *Ann. Pharm. Fr.*, **28,** 289(1970); through *Chem. Abstr.*, **73,** 123490z(1970).
(282) E. Borzunov and S. Shevchenko, *Farm. Zh. (Kiev)*, **25,** 60(1970); through *Chem. Abstr.*, **73,** 28873t(1970).
(283) P. Fuchs, *Arch. Pharm.*, **303,** 471(1970); through *Chem. Abstr.*, **73,** 48528n(1970).
(284) N. Armstrong and R. Haines-Nutt, *J. Pharm. Pharmacol.*, **22,** 8S(1970).
(285) N. A. Armstrong and R. V. Griffiths, *Pharm. Acta Helv.*, **45,** 583(1970); through *Chem. Abstr.*, **73,** 91229c(1970).
(286) N. Armstrong and R. Griffiths, *ibid.*, **45,** 692(1970); through *Chem. Abstr.*, **73,** 123497g(1970).
(287) J. E. Rees, *J. Pharm. Pharmacol.*, **22,** 245(1970).
(288) D. Travers and M. Merriman, *ibid.*, **22,** 11S(1970).
(289) M. J. Juslin, *Farm. Aikak.*, **78,** 201(1969); through *Chem. Abstr.*, **73,** 7170w(1970).
(290) O. Alpar, J. Hersey, and E. Shotton, *J. Pharm. Pharmacol.*, **22,** 1S(1970).
(291) N. L. Henderson and A. J. Bruno, *J. Pharm. Sci.*, **59,** 1336(1970).
(292) P. O. Bremer, B. Kolstad, and P. Finholt, *Medd. Nor. Farm. Selsk.*, **31,** 67(1969); through *Chem. Abstr.*, **73,** 7175b(1970).
(293) P. Ionescu-Stoian and P. Ban, *Farmacia (Bucharest)*, **18,** 273(1970); through *Chem. Abstr.*, **73,** 69785j(1970).
(294) P. Ionescu-Stoian, P. Ban, and I. Andrei, *ibid.*, **18,** 385 (1970); through *Chem. Abstr.*, **73,** 133967z(1970).
(295) T. Eaves and T. Jones, *J. Pharm. Pharmacol.*, **22,** 594 (1970).
(296) K. Ridgway, M. Aulton, and P. Rosser, *ibid.*, **22,** 70S (1970).
(297) J. Rees and E. Shotton, *ibid.*, **22,** 17S(1970).
(298) J. Rees, J. Hersey, and E. Cole, *ibid.*, **22,** 64S(1970).
(299) J. T. Fell and J. M. Newton, *J. Pharm. Sci.*, **59,** 688(1970).
(300) J. Fell and J. Newton, *J. Pharm. Pharmacol.*, **22,** 247 (1970).
(301) D. Ganderton and R. Fraser, *ibid.*, **22,** 95S(1970).
(302) D. Ganderton and A. Selkirk, *ibid.*, **22,** 345(1970).
(303) A. Selkirk and D. Ganderton, *ibid.*, **22,** 79S(1970).
(304) *Ibid.*, **22,** 86S(1970).
(305) M. V. Shteingart, I. D. Osipova, S. A. Nosovitskaya, and E. E. Borzunov, *Farmatsiya*, **19,** 17(1970); through *Chem. Abstr.*, **73,** 7129q(1970).
(306) G. Hirata, *Yakugaku Zasshi*, **90,** 114(1970).
(307) *Ibid.*, **90,** 661(1970).
(308) J. A. Wood and S. W. Harder, *Can. J. Pharm. Sci.*, **5,** 18(1970).
(309) S. W. Harder, D. A. Zuck, and J. A. Wood, *J. Pharm. Sci.*, **59,** 1787(1970).
(310) J. T. Carstensen, A. Koff, J. B. Johnson, and S. H. Rubin, *ibid.*, **59,** 553(1970).
(311) A. Heyd and J. L. Kanig, *ibid.*, **59,** 1171(1970).
(312) R. J. Lantz, Jr., A. Bailey, and M. J. Robinson, *ibid.*, **59,** 1174(1970).
(313) S. S. Kornblum and B. Lopez, *ibid.*, **59,** 1016(1970).
(314) M. Baichwal and J. Lalla, *Indian J. Technol.*, **8,** 55(1970); through *Chem. Abstr.*, **73,** 38510m(1970).
(315) J. Sajvera, *Cesk. Farm.*, **18,** 114(1969); through *Chem. Abstr.*, **72,** 35741f(1970).
(316) K. Gueven and P. Cinici, *Eczacilik Bul.*, **11,** 56(1969); through *Chem. Abstr.*, **72,** 24573b(1970).
(317) B. E. Jones, *Mfg. Chem. Aerosol News*, **41,** 53(1970).
(318) K. Klein, *Chem. Tech. Ind.*, **64,** 849(1968); through *Chem. Abstr.*, **73,** 123821h(1970).
(319) K. Karlsson and L. Spring, *J. Mater. Sci.*, **5,** 340(1970); through *Chem. Abstr.*, **73,** 29281k(1970).
(320) K. Srivastava, F. Wright, S. Khanna, I. Krishan, and R. Nayar, *Can. J. Chem.*, **48,** 3716(1970).
(321) R. J. Nessel, H. M. Apelian, and J. Blodinger, *J. Pharm. Sci.*, **59,** 254(1970).
(322) L. Garcia and E. Gulden, *SAFYBI*, **8,** 252(1968); through *Chem. Abstr.*, **73,** 28866t(1970).
(323) K. Ridgway and J. A. Hersey, *Mfg. Chem. Aerosol News*, **41,** 35(1970).
(324) A. Kassem and A. El-Gendy, *Bull. Fac. Pharm., Cairo Univ.*, **8,** 233(1969); through *Chem. Abstr.*, **73,** 69797q(1970).
(325) A. Alekseev, Y. Yanovich, and G. Anosov, *Tr. Nauch. Konf. Tomsk. Otd. Vses. Khim. Obshchest., 1st*, **1968,** 28; through *Chem. Abstr.*, **73,** 80475d(1970).
(326) S. Enomoto and S. Tanada, *Zairyo*, **19,** 592(1970); through *Chem. Abstr.*, **73,** 69778j(1970).
(327) J. A. Hersey, *J. Soc. Cosmet. Chem.*, **21,** 259(1970).
(328) T. Stozek, L. Krowczynski, and E. Osman, *Farm. Pol.*, **26,** 361(1970); through *Chem. Abstr.*, **73,** 133968a(1970).
(329) N. Lindberg, *Acta Pharm. Suecica*, **7,** 23(1970); through *Chem. Abstr.*, **72,** 136376w(1970).
(330) L. Geryser, *Cesk. Farm.*, **19,** 74(1970); through *Chem. Abstr.*, **73,** 69799s(1970).
(331) P. Cox and F. Spanjers, *Pharm. Weekbl.*, **105,** 681(1970); through *Chem. Abstr.*, **73,** 38509t(1970).
(332) R. D. Gibson and J. E. Tingstad, *J. Pharm. Sci.*, **59,** 426(1970).

(333) B. Zaputryaev and H. El-Banna, *Khim.-Farm. Zh.*, **4,** 23(1970); through *Chem. Abstr.*, **73,** 133970v(1970).
(334) J. C. Stone, *J. Pharm. Sci.*, **59,** 1364(1970).
(335) B. Zaputryaev and K. El-Banna, *Khim.-Farm. Zh.*, **4,** 46(1970); through *Chem. Abstr.*, **73,** 80460v(1970).
(336) L. IstratescuGuti and E. Manolache, *Farmacia (Bucharest)*, **18,** 117(1970); through *Chem. Abstr.*, **73,** 80462x(1970).
(337) S. Jayasinghe, N. Pilpel, and C. Harwood, *Mater. Sci. Eng.*, **5,** 287(1970); through *Chem. Abstr.*, **73,** 70173q(1970).
(338) R. Huettenrauch and W. Roos, *Pharmazie*, **25,** 259(1970); through *Chem. Abstr.*, **73,** 123504g(1970).
(339) B. Selmeczi and M. Liptak, *Sci. Pharm.*, **37,** 284(1969); through *Chem. Abstr.*, **72,** 82941f(1970).
(340) E. Sandell, *Acta Pharm. Suecica*, **7,** 55(1970); through *Chem. Abstr.*, **72,** 136372s(1970).
(341) S. Lin, J. Menig, and C. J. Swartz, *J. Pharm. Sci.*, **59,** 989(1970).
(342) A. Kassem, A. El-Gendy, and N. Rifaat, *Bull. Fac. Pharm., Cairo Univ.*, **8,** 161(1969); through *Chem. Abstr.*, **73,** 38511n(1970).
(343) Z. Farooqi, *Pak. J. Sci.*, **21,** 70(1969); through *Chem. Abstr.*, **73,** 133969b(1970).
(344) J. Maley, M. Chalabala, and M. Heliova, *Acta Fac. Pharm. Univ. Comeniana*, **16,** 113(1968); through *Chem. Abstr.*, **72,** 6225k (1970).
(345) M. Hoffman, J. Martin, and M. Hoffman, *Bull. Soc. Pharm. Nancy*, **82,** 32(1969); through *Chem. Abstr.*, **72,** 70613n (1970).
(346) U. Hammer, *Arch. Pharm. Chemi*, **76,** 1019(1969); through *Chem. Abstr.*, **73,** 28865s(1970).
(347) J. Delporte, *Pharm. Acta Helv.*, **45,** 525(1970); through *Chem. Abstr.*, **73,** 80419p(1970).
(348) E. Pandula and B. Kovacs, *Acta Pharm. Hung.*, **40,** 25 (1970); through *Chem. Abstr.*, **73,** 69809v(1970).
(349) M. Dittgen, H. Kala, and H. Moldenhauer, *Pharmazie*, **25,** 349(1970); through *Chem. Abstr.*, **73,** 112918u(1970).
(350) N. A. Muzaffar, *Pak. J. Sci.*, **21,** 72(1969); through *Chem. Abstr.*, **73,** 112872z(1970).
(351) M. Ageeva, *Khim.-Farm. Zh.*, **4,** 40(1970); through *Chem. Abstr.*, **73,** 69573x(1970).
(352) L. Van Herle, *Farmaco, Ed. Prat.*, **24,** 745(1969); through *Chem. Abstr.*, **72,** 136310v(1970).
(353) A. G. Frederickson, *AIChE J.*, **16,** 436(1970); through *Chem. Abstr.*, **73,** 18858c(1970).
(354) J. E. Carless and J. R. Nixon, *J. Soc. Cosmet. Chem.*, **21,** 427(1970).
(355) J. T. Carstensen and K. S. Su, *J. Pharm. Sci.*, **59,** 666 (1970).
(356) *Ibid.*, **59,** 671(1970).
(357) B. Matthews and C. Rhodes, *Pharm. Acta Helv.*, **45,** 52 (1970); through *Chem. Abstr.*, **72,** 35753m(1970).
(358) A. Chakravarti and C. C. Dell, *Powder Technol.*, **3,** 287 (1970).
(359) R. D. C. Jones, B. A. Matthews, and C. T. Rhodes, *J. Pharm. Sci.*, **59,** 518(1970).
(360) B. Ecanow and H. Takruri, *ibid.*, **59,** 1848(1970).
(361) A. Moes, *Pharm. Acta Helv.*, **45,** 101(1970); through *Chem. Abstr.*, **72,** 82930b(1970).
(362) P. Rohdewald, *Sci. Pharm.*, **37,** 257(1969); through *Chem. Abstr.*, **72,** 82931c(1970).
(363) *Ibid.*, **37,** 273(1969); through *Chem. Abstr.*, **72,** 82932d (1970).
(364) *Ibid.*, **38,** 1(1970); through *Chem. Abstr.*, **73,** 7188h(1970).
(365) *Ibid.*, **38,** 8(1970); through *Chem. Abstr.*, **73,** 7189j(1970).
(366) B. A. Matthews and C. T. Rhodes, *J. Colloid Interface Sci.*, **32,** 332(1970).
(367) *Ibid.*, **32,** 339(1970).
(368) P. Joos and R. Ruyssen, *J. Pharm. Belg.*, **25,** 133(1970); through *Chem. Abstr.*, **73,** 69818x(1970).
(369) B. A. Matthews and C. T. Rhodes, *J. Pharm. Sci.*, **59,** 521(1970).
(370) M. Nakagaki, S. Kawamura, and J. Terao, *Yakugaku Zasshi*, **90,** 699(1970).
(371) M. Nakagaki and S. Kawamura, *ibid.*, **90,** 1226(1970).
(372) R. Calcinari, *Farmaco, Ed. Prat.*, **25,** 24(1970); through *Chem. Abstr.*, **72,** 93316g(1970).
(373) P. Braeckman, *Gyogyszereszet*, **14,** 161(1970); through *Chem. Abstr.*, **73,** 69751v(1970).
(374) P. Hoepfner, *Chem. Phys. Appl. Surface Active Subst., Proc. Int. Congr., 4th*, **2,** 1289(1964); through *Chem. Abstr.*, **72,** 25283u(1970).
(375) W. W. Binns, G. Blunden, W. F. H. McLean, and G. Richardson, *Pharm. J.*, **204,** 7(1970).
(376) C. Giles and D. Duff, *J. Soc. Dyers Colour*, **86,** 405(1970); through *Chem. Abstr.*, **73,** 123882d(1970).
(377) H. Hadert, *Chem.-Tech. Ind.*, **65,** 638(1969); through *Chem. Abstr.*, **72,** 36056y(1970).
(378) M. Baichwal and A. Phadnis, *Indian J. Pharm.*, **31,** 106 (1969); through *Chem. Abstr.*, **72,** 24554w(1970).
(379) R. Kolosyuk, N. Vdovenko, Y. Ishchuk, and A. Zkukova, *Kolloid Zh.*, **32,** 706(1970); through *Chem. Abstr.*, **73,** 132253b (1970).
(380) L. Rafinski, S. Perz, and M. Zagalak, *Acta Pol. Pharm.*, **27,** 41(1970); through *Chem. Abstr.*, **73,** 80455x(1970).
(381) S. Merchant and E. Rosauer, *Clays Clay Miner.*, **17,** 289(1969); through *Chem. Abstr.*, **72,** 70972d(1970).
(382) S. Kanungo and P. De, *Indian J. Technol.*, **8,** 71(1970); through *Chem. Abstr.*, **73,** 38893p(1970).
(383) G. E. Schumacher, *Amer. J. Hosp. Pharm.*, **27,** 64(1970).
(384) I. Schmolka, *Fed. Proc., Fed. Amer. Soc. Exp. Biol.*, **29,** 1717(1970); through *Chem. Abstr.*, **73,** 80846a(1970).
(385) C. Mathis, *Praep. Pharm.*, **6,** 67(1970); through *Chem. Abstr.*, **73,** 132242x(1970).
(386) S. Rodriguez, *Quimia (Barcelona)*, **185,** 9(1969); through *Chem. Abstr.*, **73,** 28767m(1970).
(387) W. J. Hackett, *Deterg. Spec.*, **6,** 28(1969); through *Chem. Abstr.*, **72,** 47762b(1970).
(388) H. S. Bean, G. H. Konning, and J. Thomas, *Amer. Perfum. Cosmet.*, **85,** 61(1970).
(389) L. M. Prince, *J. Soc. Cosmet. Chem.*, **21,** 193(1970).
(390) V. Korzans, *Probl. Parenter. Pitan., Mater. Soveshch., 1st*, **1967,** 21; through *Chem. Abstr.*, **73,** 80427q(1970).
(391) T. M. Riddick, *Amer. Perfum. Cosmet.*, **85,** 31(1970).
(392) B. Mulley and J. Marland, *J. Pharm. Pharmacol.*, **22,** 243(1970).
(393) K. J. Lissant, *J. Soc. Cosmet. Chem.*, **21,** 141(1970).
(394) M. Kerker, *Amer. Perfum. Cosmet.*, **85,** 43(1970).
(395) D. P. Kessler and J. L. York, *AIChE J.*, **16,** 369(1970); through *Chem. Abstr.*, **73,** 18855z(1970).
(396) S. Friberg and L. Mandell, *J. Pharm. Sci.*, **59,** 1001(1970).
(397) S. Friberg and I. Wilton, *Amer. Perfum. Cosmet.*, **85,** 27(1970).
(398) E. R. Garrett, *J. Soc. Cosmet. Chem.*, **21,** 393(1970).
(399) T. Mitsui, *Shikizai Kyokaishi*, **42,** 506(1969); through *Chem. Abstr.*, **73,** 18753q(1970).
(400) H. Saito and K. Shinoda, *J. Colloid Interface Sci.*, **32,** 647(1970).
(401) S. Matsumoto and P. Sherman, *ibid.*, **33,** 294(1970).
(402) J. Jombik, Z. Gruntova, and P. Schiller, *Pharm. Ind.*, **31,** 950(1969); through *Chem. Abstr.*, **73,** 7190c(1970).
(403) L. Bardet, H. Delonca, J. Lacoste, and H. Maillols, *Trav. Soc. Pharm. Montpellier*, **29,** 101(1969); through *Chem. Abstr.*, **72,** 47763c(1970).
(404) M. Aoki, N. Yata, K. Kato, and I. Yoshioka, *Chem. Pharm. Bull.*, **18,** 36(1970).
(405) A. Saadat and K. Leupin, *Pharm. Acta Helv.*, **45,** 119 (1970); through *Chem. Abstr.*, **72,** 93317h(1970).
(406) K. Horikawa and S. Masuyama, *Yukagaku*, **18,** 808 (1969); through *Chem. Abstr.*, **72,** 47764d(1970).
(407) B. W. Barry and G. M. Saunders, *J. Colloid Interface Sci.*, **34,** 300(1970).
(408) B. W. Barry, *ibid.*, **32,** 551(1970).
(409) F. Talman and E. Rowan, *J. Pharm. Pharmacol.*, **22,** 338(1970).
(410) *Ibid.*, **22,** 417(1970).
(411) *Ibid.*, **22,** 535(1970).
(412) F. Kunertova and J. Dlouha, *Veda Vyzk. Prum. Potravin*, **18,** 241(1968); through *Chem. Abstr.*, **72,** 24500a(1970).
(413) R. Voigt and W. Droeseler, *Pharmazie*, **24,** 622(1969); through *Chem. Abstr.*, **72,** 59034d(1970).
(414) E. Pandula, E. Farkas, P. Keseru, and A. Csontos, *Acta Pharm. Hung.*, **40,** 211(1970); through *Chem. Abstr.*, **73,** 133975a (1970).

(415) E. Pandula, E. Farkas, P. Keseru, and A. Csontos, *ibid.*, **40,** 217(1970); through *Chem. Abstr.*, **73,** 133976b(1970).

(416) F. Lachampt, *Amer. Perfum. Cosmet.*, **85,** 27(1970).

(417) G. Rimlinger, *ibid.*, **85,** 29 (1970).

(418) J. Mizrahi and E. Barnea, *Brit. Chem. Eng.*, **15,** 497 (1970); through *Chem. Abstr.*, **73,** 29244a(1970).

(419) A. Abramzon and Z. Slavina, *Kolloid Zh.*, **31,** 635(1969); through *Chem. Abstr.*, **72,** 25211u(1970).

(420) A. Matyok and Z. Csath-Stincel, *Farmacia*, **18,** 107(1970); through *Chem. Abstr.*, **73,** 18752p(1970).

(421) L. Sujbert and F. Fodor, *Acta Pharm. Hung.*, **40,** 5(1970); through *Chem. Abstr.*, **73,** 69806s(1970).

(422) G. Rimlinger, *Parfum., Cosmet., Savons*, **13,** 366(1970); through *Chem. Abstr.*, **73,** 59220g(1970).

(423) E. Madeira, *Rev. Brasil. Farm.*, **50,** 221(1969); through *Chem. Abstr.*, **72,** 125044k(1970).

(424) A. Sheludko, *God. Sofi. Univ., Khim. Fak.*, **62,** 93(1967); through *Chem. Abstr.*, **73,** 134171x(1970).

(425) R. Huettenrauch, *Pharmazie*, **25,** 169(1970); through *Chem. Abstr.*, **73,** 28874u(1970).

(426) M. Nakano and N. K. Patel, *J. Pharm. Sci.*, **59,** 985(1970).

(427) O. I. Ryaposova and B. V. Nazarov, *Farmatsiya (Moscow)*, **19,** 17(1970); through *Chem. Abstr.*, **73,** 59281c(1970).

(428) Z. Gruntova, M. Mandak, and K. Duckova, *Acta Fac. Pharm., Univ. Comeniana*, **17,** 163(1969); through *Chem. Abstr.*, **73,** 112924t(1970).

(429) K. Khristov, M. Gluzman, P. Todorova, and B. Dashevskaya, *Pharmazie*, **25,** 344(1970); through *Chem. Abstr.*, **73,** 80467c (1970).

(430) C. Fuehrer, *Arch. Klin. Exp. Dermatol.*, **237,** 251(1968); through *Chem. Abstr.*, **72,** 136379z(1970).

(431) M. J. Busse, P. Hunt, K. A. Lees, P. N. D. Maggs, and T. M. McCarthy, *Brit. J. Dermatol., Suppl.*, **81,** 103(1969); through *Chem. Abstr.*, **72,** 103690r(1970).

(432) E. Hansen and C. Wiese, *Arch. Pharm. Chemi*, **76,** 889 (1969); through *Chem. Abstr.*, **72,** 24583e(1970).

(433) A. Rub-Saidac, O. Bugnariu, V. Filipas, V. Ciocanelea, and I. Oprean, *Pharmazie*, **25,** 194(1970); through *Chem. Abstr.*, **73,** 59280b(1970).

(434) A. Rub-Saidac, O. Bugnariu, V. Filipas, V. Ciocanelea, I. Tirlea, L. Cucu-Cabadaief, and I. Oprean, *ibid.*, **25,** 252(1970); through *Chem. Abstr.*, **73,** 102020f(1970).

(435) G. Hangay, *Acta Pharm. Hung.*, **40,** 17(1970); through *Chem. Abstr.*, **73,** 69793k(1970).

(436) *Ibid.*, **40,** 75(1970); through *Chem. Abstr.*, **73,** 69804q (1970).

(437) *Ibid.*, **40,** 116(1970); through *Chem. Abstr.*, **73,** 38508s (1970).

(438) G. Myers and G. A. Leslie, *Can. J. Pharm. Sci.*, **4,** 64 (1969); through *Chem. Abstr.*, **72,** 47336r(1970).

(439) F. Martino, *Rev. Brasil. Farm.*, **50,** 217(1969); through *Chem. Abstr.*, **72,** 125043j(1970).

(440) G. Regdon and I. Kovacs, *Deut. Apoth.-Ztg.*, **109,** 1893 (1969); through *Chem. Abstr.*, **72,** 70611k(1970).

(441) S. Kazushige, S. Matsumoto, T. Watanabe, and S. Ono, *Kogyo Kagaku Zasshi*, **73,** 774(1970); through *Chem. Abstr.*, **73,** 69730n(1970).

(442) K. Khristov and L. Draganova, *Farmatsiya*, **19,** 1(1969); through *Chem. Abstr.*, **73,** 7187g(1970).

(443) Z. Olszewski and A. Kubis, *Acta Pol. Pharm.*, **26,** 447 (1969); through *Chem. Abstr.*, **72,** 82943h(1970).

(444) G. Tsagareishvili, G. Bashura, A. Lekhan, and I. Kovalev, *Soobshch. Akad. Nauk Gruz. SSR*, **56,** 345(1969); through *Chem. Abstr.*, **72,** 82942g(1970).

(445) T. Grudov, *Dermatol. Venerol. (Sofia)*, **8,** 232(1969); through *Chem. Abstr.*, **73,** 28755f(1970).

(446) W. Horsch and J. Koegel, *Pharmazie*, **25,** 434(1970); through *Chem. Abstr.*, **73,** 112922r(1970).

(447) R. Dynakowski and R. Figurski, *Farm. Pol.*, **25,** 987 (1969); through *Chem. Abstr.*, **73,** 7186f(1970).

(448) Z. Elsner, *Diss. Pharm. Pharmacol.*, **21,** 341(1969); through *Chem. Abstr.*, **72,** 15727c(1970).

(449) M. Baichwal and V. Lohit, *J. Pharm. Pharmacol.*, **22,** 427(1970).

(450) B. Bochev, P. Zikolov, and T. Trandafilov, *Farmatsiya*, **20,** 22(1970); through *Chem. Abstr.*, **73,** 112915r(1970).

(451) G. Mezey and G. Kedvessy, *Acta Pharm. Hung.*, **40,** 200(1970); through *Chem. Abstr.*, **73,** 133966y(1970).

(452) H. Leszczynska-Bakal and Z. Elsner, *Farm. Pol.*, **25,** 427 (1969); through *Chem. Abstr.*, **72,** 6224j(1970).

(453) G. Ritschel-Beurlin, *Praep. Pharm.*, **5,** 6(1969); through *Chem. Abstr.*, **72,** 136380t(1970).

(454) T. Cieszynski, *Farm. Pol.*, **26,** 207(1970); through *Chem. Abstr.*, **73,** 48530g(1970).

(455) V. Bhavnagri and P. Speiser, *Praep. Pharm.*, **6,** 61(1970); through *Chem. Abstr.*, **73,** 38519w(1970).

(456) H. W. Puffer and P. A. Barnett, *J. Pharm. Sci.*, **59,** 848 (1970).

(457) C. Leering, J. T. W. Kamps, and E. B. L. M. Van-Nispen tot Pannerden, *Pharm. Weekbl.*, **105,** 30(1970); through *Chem. Abstr.*, **72,** 103691s(1970).

(458) I. Ballo, *Rev. Med. (Tirgu-Mures)*, **15,** 219(1969); through *Chem. Abstr.*, **72,** 35751j(1970).

(459) W. Wiegrebe, *Deut. Apoth.-Ztg.*, **109,** 1672(1969); through *Chem. Abstr.*, **72,** 35752k(1970).

(460) Y. Khadzhai and A. Nikolaeva, *Farmatsiya (Moscow)*, **19,** 34(1970); through *Chem. Abstr.*, **73,** 133971w(1970).

(461) A. Kassem, I. El-Din, and A. El-Shamy, *Bull. Fac. Pharm., Cairo Univ.*, **8,** 193(1969); through *Chem. Abstr.*, **73,** 38520q(1970).

(462) H. Renker and F. Neuwald, *Pharm. Ind.*, **32,** 300(1970); through *Chem. Abstr.*, **73,** 69803p(1970).

(463) O. G. Raabe, *AEC Symp. Ser.*, **18,** 123(1970); through *Chem. Abstr.*, **73,** 59232n(1970).

(464) A. Herzka, *J. Soc. Cosmet. Chem.*, **21,** 553(1970).

(465) K. Bergwein, *Kosmet.-Perfum-Drogen Rundsch.*, **16,** 142(1969); through *Chem. Abstr.*, **72,** 82884q(1970).

(466) K. Janes and M. Zahradnik, *Veda Vysk. Prum. Potravin*, **19,** 221(1969); through *Chem. Abstr.*, **72,** 124989k(1970).

(467) B. D. Joyner and C. L. Holmes, *Mfg. Chem. Aerosol News*, **41,** 48(1970).

(468) *Ibid.*, **41,** 81(1970).

(469) P. Sanders, *Aerosol Age*, **14,** 34(1969); through *Chem. Abstr.*, **72,** 25175k(1970).

(470) K. Scrader, *Dragoco Rep.*, **16,** 223(1969); through *Chem. Abstr.*, **72,** 93276u(1970).

(471) W. F. Kirk, *Mfg. Chem. Aerosol News*, **41,** 31(1970).

(472) L. Tobler, *Kosmet.-Perfum-Drogen Rundsch.*, **17,** 45(1970); through *Chem. Abstr.*, **73,** 48488z(1970).

(473) K. Wegener, *Riechst., Aromen, Koerperpflegem.*, **20,** 41 (1970); through *Chem. Abstr.*, **72,** 93286x(1970).

(474) P. A. Sanders, *J. Soc. Cosmet. Chem.*, **21,** 377(1970).

(475) J. J. Sciarra and R. Gidwani, *ibid.*, **21,** 667(1970).

(476) W. Eckardt, *ibid.*, **21,** 281(1970).

(477) L. T. Flanner, *ibid.*, **21,** 661(1970).

(478) R. F. Robey, *ibid.*, **21,** 183(1970).

(479) R. Goldman, *Drug Cosmet. Ind.*, **107,** 52(1970).

(480) V. Boyanova, *Farmatsiya (Sofia)*, **19,** 63(1969); through *Chem. Abstr.*, **72,** 35693s(1970).

(481) G. Ceschel, *Cron. Farm.*, **12,** 334(1969); through *Chem. Abstr.*, **72,** 136301t(1970).

(482) J. R. Robinson and S. P. Eriksen, *J. Pharm. Sci.*, **59,** 1796(1970).

(483) W. E. Smith, J. D. Buehler, and M. J. Robinson, *ibid.*, **59,** 776(1970).

(484) S. C. Khanna, T. Jecklin, and P. Speiser, *ibid.*, **59,** 614 (1970).

(485) L. A. Luzzi, M. A. Zoglio, and H. V. Maulding, *ibid.*, **59,** 338(1970).

(486) K. Froemming and R. Sandmann, *Arch. Pharm. (Weinheim)*, **303,** 371(1970); through *Chem. Abstr.*, **73,** 28855p(1970).

(487) A. Widmann, F. Eiden, and J. Tenczer, *Arzneim.-Forsch.*, **20,** 283(1970); through *Chem. Abstr.*, **72,** 136368v(1970).

(488) S. Banerjee, A. K. Mukherjee, and A. K. Halder, *J. Pharm. Sci.*, **59,** 273(1970).

(489) W. Ebert, R. Mossis, S. Rowles, H. Russell, G. Born, and J. Christian, *ibid.*, **59,** 1409(1970).

(490) R. Schuhmann and H. Taubert, *Acta Biol. Med. Ger.*, **24,** 897(1970); through *Chem. Abstr.*, **73,** 123486c(1970).

(491) A. S. Lifchez and A. Scommegna, *Fert. Steril.*, **21,** 426 (1970); through *Chem. Abstr.*, **73,** 28884x(1970).

(492) P. Kratochvil, G. Benagiano, and F. Kincl, *Steroids*, **15,** 505(1970); through *Chem. Abstr.*, **72,** 136369w(1970).

(493) S. Friedman, S. Koide, and F. Kincl, *ibid.*, **15,** 679(1970); through *Chem. Abstr.*, **73,** 28870q(1970).
(494) F. Kincl, K. Sundaram, C. Chang, and H. Rudel, *Acta Endocrinol. (Copenhagen)*, **64,** 253(1970); through *Chem. Abstr.*, **73,** 28867u(1970).
(495) W. Ritschel and G. Ritschel-Beurlin, *Praep. Pharm.*, **5,** 59(1969); through *Chem. Abstr.*, **72,** 136367u(1970).
(496) L. Hollister, S. Curry, J. Derr, and S. Kanter, *Clin. Pharmacol. Ther.*, **11,** 49(1970).
(497) S. Kotenko, V. Pochinok, M. Tarakhovskii, and A. Fadeicheva, *Farm. Zh. (Kiev)*, **25,** 53(1970); through *Chem. Abstr.*, **73,** 69786k(1970).
(498) V. Dallavalle and G. Gal, *Farmaco, Ed. Prat.*, **25,** 440 (1970); through *Chem. Abstr.*, **73,** 69796p(1970).
(499) M. Niemisto, *Scand. J. Resp. Dis. Suppl.*, **71,** 64(1970); through *Chem. Abstr.*, **73,** 75575g(1970).
(500) H. Andersen and H. Holmen-Christensen, *Dan. Tidsskr. Farm.*, **43,** 117(1969); through *Chem. Abstr.*, **72,** 20219t(1970).
(501) M. Chalabala and L. Starha, *Acta Fac. Pharm., Univ. Comeniana*, **17,** 177(1969); through *Chem. Abstr.*, **73,** 112917t (1970).
(502) G. Cotta and A. Arancibia, *Farmco, Ed. Prat.*, **24,** 766 (1969); through *Chem. Abstr.*, **72,** 136370q(1970).
(503) P. Spinelli and M. Ciuffi, *Boll. Chim. Farm.*, **109,** 205 (1970); through *Chem. Abstr.*, **73,** 69794m(1970).
(504) E. S. Allen, *Curr. Ther. Res., Clin. Exp.*, **11,** 745(1969); through *Chem. Abstr.*, **72,** 59032b(1970).
(505) P. G. I. Lauffer, *Amer. Perfum. Cosmet.*, **85,** 27(1970).
(506) D. Wurster, *Develop. Saf. More Eff. Drugs, Symp.*, **1967,** 121; through *Chem. Abstr.*, **72,** 24574c(1970).
(507) B. Ellot, *Kosmet.-Parfum-Drogen Rundsch.*, **17,** 33(1970); through *Chem. Abstr.*, **73,** 48487y(1970).
(508) H. Mima, H. Nomura, Y. Imai, and H. Takashima, *Bitamin*, **41,** 387 (1970); through *Chem. Abstr.*, **73,** 102016j(1970).
(509) O. Jacobi, *Amer. Perfum. Cosmet.*, **85,** 25(1970).
(510) S. I. Kreps, *ibid.*, **85,** 37(1970).
(511) S. L. Yankell, G. N. Martin, H. Piechuta, W. A. Hockett, and M. M. Dolan, *J. Soc. Cosmet. Chem.*, **21,** 607(1970).
(512) W. Greber, *Kosmet.-Parfum-Drogen Rundsch.*, **16,** 112 (1969); through *Chem. Abstr.*, **72,** 47302b(1970).
(513) G. Laporte, *Amer. Perfum. Cosmet.*, **85,** 47(1970).
(514) J. N. Bollinger and L. L. Seelig, Jr., *J. Soc. Cosmet. Chem.*, **21,** 613(1970).
(515) H. Hadert, *Riechst., Aromen, Koerperpflegem.*, **18,** 186 (1968); through *Chem. Abstr.*, **72,** 82883p(1970).
(516) H. Fueher, *Kosmetic*, **43,** 63(1970); through *Chem. Abstr.*, **72,** 93274s(1970).
(517) H. Baumann, *Chem. Phys. Appl. Surface Active Subst., Proc. Int. Congr., 4th*, **3,** 361(1964); through *Chem. Abstr.*, **72,** 6229q(1970).
(518) L. G. Felty, J. H. McAteer, and M. Coopersmith, *Drug Cosmet. Ind.*, **106,** 42(1970).
(519) A. E. Young, *Mfg. Chem. Aerosol News*, **41,** 27(1970).
(520) S. Most and A. Katz, *Amer. Perfum. Cosmet.*, **85,** 67(1970).
(521) D. E. Alguire, *ibid.*, **85,** 31(1970).
(522) D. L. Wedderburn, *ibid.*, **85,** 49(1970).
(523) C. R. Woodward, Jr., and R. F. McNamara, *ibid.*, **85,** 73(1970).
(524) E. E. Boehm and D. N. Maddox, *ibid.*, **85,** 31(1970).
(525) I. R. Gucklhorn, *Mfg. Chem. Aerosol News*, **41,** 30(1970).
(526) *Ibid.*, **41,** 26(1970).
(527) *Ibid.*, **41,** 34(1970).
(528) *Ibid.*, **41,** 44(1970).
(529) *Ibid.*, **41,** 51(1970).
(530) *Ibid.*, **41,** 28(1970).
(531) *Ibid.*, **41,** 82(1970).
(532) *Ibid.*, **41,** 49(1970).
(533) *Ibid.*, **41,** 48(1970).
(534) *Ibid.*, **41,** 50(1970).
(535) W. F. Schorr, *Amer. Perfum. Cosmet.*, **85,** 39(1970).
(536) C. K. von Fenyes, *ibid.*, **85,** 91(1970).
(537) W. Henley and N. Sonntag, *ibid.*, **85,** 95(1970).
(538) W. Eckardt, *ibid.*, **85,** 83(1970).
(539) F. Benzinger and S. Hohnjec-Mihaljinac, *Sci. Pharm.*, **38,** 107(1970); through *Chem. Abstr.*, **73,** 69779k(1970).
(540) E. Tuttle, C. Phares, and R. F. Chiostri, *Amer. Perfum. Cosmet.*, **85,** 87(1970).
(541) P. A. Berke and W. E. Rosen, *ibid.*, **85,** 55(1970).
(542) D. C. McLeod, *Amer. J. Hosp. Pharm.*, **27,** 742(1970).
(543) J. Autian, *Bull. Parenteral Drug Ass.*, **22,** 276(1968); through *Chem. Abstr.*, **73,** 38450s(1970).
(544) N. Nagabhushan, R. Coutts, and N. Patel, *Can. J. Pharm. Sci.*, **4,** 79(1969); through *Chem. Abstr.*, **72,** 70615q(1970).
(545) T. J. McCarthy, *Pharm. Weekbl.*, **105,** 557(1970); through *Chem. Abstr.*, **73,** 18464w(1970).
(546) T. J. McCarthy, *ibid.*, **105,** 1139(1970); through *Chem. Abstr.*, **73,** 123477a(1970).
(547) N. K. Patel and N. Nagabhushan, *J. Pharm. Sci.*, **59,** 264(1970).
(548) A. E. Polack, M. S. Roberts, and F. Schumann, *Amer. J. Hosp. Pharm.*, **27,** 638(1970).
(549) A. Calo, A. Sampaolo, G. Cavazzutti, B. TucciBucci, and G. Esposito, *Boll. Chim. Farm.*, **109,** 100(1970); through *Chem. Abstr.*, **73,** 38523t(1970).
(550) F. Neuwald and D. Scheel, *Pharm. Ind.*, **31,** 879(1969); through *Chem. Abstr.*, **72,** 82946m(1970).
(551) F. Neuwald and K. Lafrenz, *ibid.*, **31,** 883(1969); through *Chem. Abstr.*, **72,** 82945k(1970).
(552) M. Sandor-Molnar and Z. Toth, *Gyogyszereszet*, **13,** 327(1969); through *Chem. Abstr.*, **72,** 24587j(1970).
(553) N. Rojas, *Rev. Colomb. Cienc. Quim.-Farm.*, **1,** 67(1969); through *Chem. Abstr.*, **73,** 123491a(1970).
(554) O. Schettino and M. La Rotonda, *Boll. Soc. Ital. Biol. Sper.*, **45,** 1337(1969); through *Chem. Abstr.*, **73,** 123494d(1970).
(555) S. C. Jolly, W. Lund, and E. G. John, *Pharm. J.*, **204,** 291(1970).
(556) E. Spingler, *Pharm. Acta Helv.*, **45,** 686(1970); through *Chem. Abstr.*, **73,** 123492b(1970).
(557) W. Ullrich, *Oesterr. Apoth. Ztg.*, **24,** 416(1970); through *Chem. Abstr.*, **73,** 80466b(1970).
(558) T. Ohsato, *Kekkaku*, **45,** 97(1970); through *Chem. Abstr.*, **73,** 38501j(1970).
(559) H. W. Fowler, *Mfg. Chem. Aerosol News*, **41,** 51(1970).
(560) A. Das, *ibid.*, **41,** 27(1970).
(561) F. R. Chase, *Drug Cosmet. Ind.*, **107,** 66(1970).
(562) J. E. P. Miles, *J. Soc. Cosmet. Chem.*, **21,** 53(1970).
(563) J. W. Conine and H. R. Hadley, *Drug. Cosmet. Ind.*, **106,** 38(1970).
(564) A. D. Reynolds, *Mfg. Chem. Aerosol News*, **41,** 40(1970).
(565) F. W. Goodhart, J. R. Draper, and F. C. Ninger, *J. Pharm. Sci.*, **59,** 540(1970).
(566) M. Summers, J. Carless, and R. Enever, *J. Pharm. Pharmacol.*, **22,** 615(1970).
(567) H. Lin and J. Guillory, *J. Pharm. Sci.*, **59,** 972(1970).
(568) R. Pfeiffer, K. Yang, and M. Tucker, *ibid.*, **59,** 1809(1970).
(569) L. Ravin, E. Shami, and E. Rattie, *ibid.*, **59,** 1290(1970).
(570) L. Shenouda, *ibid.*, **59,** 785(1970).
(571) D. Simmons, R. Ranz, P. Picotte, and S. Szabolcs, *Can. J. Pharm. Sci.*, **5,** 49(1970).
(572) T. Kuriyama, M. Nobutoki, and M. Nakanishi, *J. Pharm. Sci.*, **59,** 1341(1970).
(573) *Ibid.*, **59,** 1344(1970).
(574) *Ibid.*, **59,** 1412(1970).
(575) K. Herzog and J. Swarbrick, *J. Pharm. Sci.*, **59,** 1759 (1970).
(576) D. Kildsig, R. Nedich, and G. Banker, *ibid.*, **59,** 1634 (1970).
(577) A. Fites, G. Banker, and V. Smolen, *ibid.*, **59,** 610(1970).
(578) H. Goodman and G. Banker, *ibid.*, **59,** 1131(1970).
(579) C. Rhodes, K. Wai, and G. Banker, *ibid.*, **59,** 1578(1970).
(580) *Ibid.*, **59,** 1583(1970).
(581) I. Hamid and C. Becker, *J. Pharm. Sci.*, **59,** 511(1970).
(582) S. Khanna and P. Speiser, *ibid.*, **59,** 1398(1970).
(583) B. McGee, D. Kennedy, and G. Walker, *ibid.*, **59,** 1430 (1970).
(584) J. Newton and G. Rowley, *J. Pharm. Pharmacol.*, **22,** 163S(1970).
(585) T. Roseman and W. Higuchi, *J. Pharm. Sci.*, **59,** 353(1970).
(586) M. Augustine and J. Swarbrick, *ibid.*, **59,** 314(1970).
(587) P. Short, E. Abbs, and C. Rhodes, *ibid.*, **59,** 995(1970).
(588) A. Thakkar, W. Wilham, and P. Demarco, *ibid.*, **59,** 281 (1970).
(589) Y. Sugiura and H. Tanaka, *Chem. Pharm. Bull.*, **18,** 746 (1970).

(590) Y. Sugiura, A. Yokoyama, and H. Tanaka, *ibid.*, **18,** 693(1970).
(591) E. Shefter, P. Sackman, W. Stephen, Jr., and E. Smissman, *J. Pharm. Sci.*, **59,** 1118(1970).
(592) S. Hem, E. Russo, S. Bahal, and R. Levi, *ibid.*, **59,** 317 (1970).
(593) H. Johnson, P. Tsakotellis, and J. DeGraw, *ibid.*, **59,** 278(1970).
(594) K. Murthy and G. Zografi, *ibid.*, **59,** 1281(1970).
(595) R. Lindstrom and A. Giaquinto, *ibid.*, **59,** 1635(1970).
(596) B. Amirov and O. Belozerova, *Khim.-Farm. Zh.*, **38,** 4(1970); through *Chem. Abstr.*, **73,** 80452u(1970).
(597) J. Fell and J. Newton, *Pharm. Acta Helv.*, **45,** 520(1970); through *Chem. Abstr.*, **73,** 80457z(1970).
(598) D. Evans, *Selec. Top. Med. Genet.*, **1969,** 69; through *Chem. Abstr.*, **72,** 20194f(1970).
(599) L. Ikenberry and H. Yasuda, *U.S. Govt. Res. Develop. Rep.*, **70,** 42(1970); through *Chem. Abstr.*, **73,** 112942x(1970).
(600) Z. Golucki, *Diss. Pharm. Pharmacol.*, **21,** 457(1969); through *Chem. Abstr.*, **72,** 35750h(1970).
(601) H. Tanaka, H. Sakurai, and A. Yokoyama, *Chem. Pharm. Bull.*, **18,** 1015(1970).
(602) E. Smith, *J. Soc. Cosmet. Chem.*, **21,** 563(1970).
(603) P. Shah and W. Moore, *J. Pharm. Sci.*, **59,** 1034(1970).
(604) J. Samyn and W. Jung, *ibid.*, **59,** 169(1970).
(605) F. Hom and J. Miskel, *ibid.*, **59,** 827(1970).
(606) M. Gibaldi, S. Feldman, and N. Weiner, *Chem. Pharm. Bull.*, **18,** 715(1970).
(607) J. Piccolo and R. Tawashi, *J. Pharm. Sci.*, **59,** 56(1970)
(608) I. Ullah and D. Cadwallader, *ibid.*, **59,** 979(1970).
(609) J. Tingstad and S. Riegelman, *ibid.*, **59,** 692(1970).
(610) C. Lerk and K. Zuurman, *J. Pharm. Pharmacol.*, **22,** 319 (1970).
(611) H. Weintraub and M. Gibaldi, *J. Pharm. Sci.*, **59,** 1792 (1970).
(612) S. Kornblum and J. Hirschorn, *ibid.*, **59,** 606(1970).
(613) S. Solvang and P. Finholt, *ibid.*, **59,** 49(1970).
(614) S. Solvang and P. Finholt, *Medd. Nor. Farm. Selsk.*, **31,** 101(1969); through *Chem. Abstr.*, **73,** 7164x(1970).
(615) A. Heyd, *J. Pharm. Sci.*, **59,** 1526(1970).
(616) A. Heyd, D. Kildsig, and G. Banker, *ibid.*, **59,** 947(1970).
(617) H. Nogami, T. Nagai, and A. Kondo, *Chem. Pharm. Bull.*, **18,** 1185(1970).
(618) *Ibid.*, **18,** 2290(1970).
(619) J. Wagner, *Drug Intel. Clin. Pharm.*, **3,** 198(1969); through *Chem. Abstr.*, **73,** 107769s(1970).
(620) *Ibid.*, **4,** 17(1970); through *Chem. Abstr.*, **72,** 82919e(1970).
(621) *Ibid.*, **4,** 32(1970); through *Chem. Abstr.*, **73,** 7100y(1970).
(622) *Ibid.*, **4,** 77(1970); through *Chem. Abstr.*, **73,** 7115g(1970).
(623) *Ibid.*, **4,** 232(1970); through *Chem. Abstr.*, **73,** 133944q (1970).
(624) C. Blezek, J. Lach, and J. Guillory, *Amer. J. Hosp. Pharm.*, **27,** 533(1970).
(625) J. Wagner, *Drug Intel. Clin. Pharm.*, **4,** 132(1970); through *Chem. Abstr.*, **73,** 75164x(1970).
(626) P. Cox and A. Mulders, *Pharm. Weekbl.*, **104,** 1629(1969); through *Chem. Abstr.*, **72,** 47334p(1970).
(627) R. Gumtow, *J. Pharm. Ed.*, **34,** 209(1970).
(628) H. Johansen and C. Wiese, *Arch. Pharm. Chemi*, **77,** 243 (1970); through *Chem. Abstr.*, **73,** 18468a(1970).
(629) E. Kristofferson, *Farm. Aikak.*, **78,** 183(1969); through *Chem. Abstr.*, **73,** 7176c(1970).
(630) J. Poole and C. Bahal, *J. Pharm. Sci.*, **59,** 1265(1970).
(631) A. Thakkar, *ibid.*, **59,** 1499(1970).
(632) D. Madan and D. Cadwallader, *ibid.*, **59,** 1362(1970).
(633) D. Bowen and K. James, *J. Pharm. Pharmacol.*, **22,** 140S (1970).
(634) J. Ostrenga and C. Steinmetz, *J. Pharm. Sci.*, **59,** 414(1970).
(635) R. Lindstrom, *ibid.*, **59,** 1695(1970).
(636) C. McDonald, *J. Pharm. Pharmacol.*, **22,** 10(1970).
(637) T. Breon and A. Paruta, *J. Pharm. Sci.*, **59,** 1306(1970).
(638) A. Ismail, M. Gouda, and M. Motawi, *ibid.*, **59,** 220(1970).
(639) M. Gouda, A. Ismail, and M. Motawi, *ibid.*, **59,** 1402 (1970).
(640) M. Donbrow, E. Azaz, and R. Hamburger, *ibid.*, **59,** 1427 (1970).
(641) F. Shihab, W. Sheffield, J. Sprowls, and J. Nematollahi, *ibid.*, **59,** 1574(1970).
(642) B. Mulley and A. Winfield, *J. Chem. Soc. (A)*, **1970,** 1459.
(643) H. Nogami, T. Nagai, and H. Umeyama, *Chem. Pharm. Bull.*, **18,** 335(1970).
(644) *Ibid.*, **18,** 328(1970).
(645) Y. Kato, *Yakugaku Zasshi*, **90,** 1464(1970).
(646) Y. Katao and Y. Sato, *ibid.*, **90,** 1187(1970).
(647) E. Minkov, M. Zakharieva, B. Botev, A. Popov, and T. Trandafilov, *Pharmazie*, **25,** 353(1970); through *Chem. Abstr.*, **73,** 101997t(1970).
(648) F. El-Khawas and N. Daabis, *ibid.*, **24,** 684(1969); through *Chem. Abstr.*, **72,** 93311b(1970).
(649) R. Alric and A. Portal, *C. R. Soc. Biol.*, **163,** 703(1969); through *Chem Abstr.*, **72,** 119715p(1970).
(650) N. Choulis, *Can. J. Pharm. Sci.*, **5,** 59(1970).
(651) T. Eckert, I. Reimann, and K. Krisch, *Arzneim.-Forsch.*, **20,** 487(1970); through *Chem. Abstr.*, **73,** 86040e(1970).
(652) H. Fujiwara and M. Kato, *Takada Kenkyusho Nempo*, **28,** 124(1969); through *Chem. Abstr.*, **72,** 59025b(1970).
(653) R. Gumtow, *J. Pharm. Ed.*, **34,** 602(1970).
(654) R. Huettenrauch, W. Suess, and U. Schmeiss, *Pharmazie*, **24,** 646(1969); through *Chem. Abstr.*, **72,** 59027d(1970).
(655) C. Iacobelli, F. Maracci, A. Margani, and M. Palmera, *Ric. Sci.*, **39,** 252(1969); through *Chem. Abstr.*, **73,** 29290n(1970).
(656) A. Hussein, A. Kassem, and M. El-Samaligy, *Bull. Fac. Pharm.*, **7,** 59(1969); through *Chem. Abstr.*, **73,** 38507r(1970).
(657) K. Konno and A. Kitahara, *Nippon Kagaku Zasshi*, **91,** 328(1970); through *Chem. Abstr.*, **73,** 26900a(1970).
(658) M. Nakagaki and N. Funasaki, *Yakugaku Zasshi*, **90,** 1310(1970).
(659) D. Ordonez, F. Salto, and J. De-la-Pena, *Quim. Ind.*, **15,** 175(1968); through *Chem. Abstr.*, **72,** 24563y(1970).
(660) A. Saleh, H. El-Shibini, and M. Motawi, *Pharmazie*, **24,** 753(1969); through *Chem. Abstr.*, **72,** 125035h(1970).
(661) F. Tokiwa, *Bull. Chem. Soc. Jap.*, **43,** 939(1970); through *Chem. Abstr.*, **72,** 134447w(1970).
(662) T. Solov'eva, L. Eremina, and R. Panich, *Kolloid. Zh.*, **31,** 749(1969); through *Chem. Abstr.*, **72,** 25352r(1970).
(663) R. Durand, *Chem. Phys. Appl. Surface Active Subst., Proc. Int. Congr., 4th*, **2,** 763(1964); through *Chem. Abstr.*, **72,** 22818m(1970).
(664) E. Sellers and J. Koch-Wesser, *Clin. Pharmacol. Ther.*, **11,** 524(1970).
(665) W. Johns and T. Bates, *J. Pharm. Sci.*, **59,** 329(1970).
(666) *Ibid.*, **59,** 788(1970).
(667) E. Lien, M. Hussain, and G. Tong, *J. Pharm. Sci.*, **59,** 865(1970).
(668) J. Dearden and E. Tomlinson, *J. Pharm. Pharmacol.*, **22,** 53S(1970).
(669) S. Curry, *ibid.*, **22,** 193(1970).
(670) I. Campbell and A. Todrick, *ibid.*, **22,** 226(1970).
(671) H. Weder and M. Bickel, *J. Pharm. Sci.*, **59,** 1505(1970).
(672) *Ibid.*, **59,** 1563(1970).
(673) K. Lunde, A. Rane, and S. Yaffe, *Clin. Pharmacol. Ther.*, **11,** 846(1970).
(674) J. Olivo, A. Southren, G. Gordon, and S. Tochimoto, *J. Clin. Endocrinol.*, **31,** 539(1970).
(675) M. Lebeau and E. Baulieu, *ibid.*, **30,** 166(1970).
(676) M. Meyer and D. Guttman, *J. Pharm. Sci.*, **59,** 39(1970).
(677) M. McDougal, *J. Amer. Pharm. Ass.*, **NS10,** 83(1970).
(678) G. Lawless, *Diss. Abstr., Int. B*, **30,** 1820(1969); through *Chem. Abstr.*, **72,** 119696h(1970).
(679) T. Mori, J. Fisher, and J. Kriss, *J. Clin. Endocrinol.*, **31,** 119(1970).
(680) T. Murakawa, Y. Wakai, Y. Toi, and M. Nishida, *Jap. J. Antibiot.*, **22,** 387(1969); through *Chem. Abstr.*, **72,** 119723q (1970).
(681) R. Penna, *J. Amer. Pharm. Ass.*, **NS10,** 66(1970).
(682) G. Phillips, D. Power, C. Robinson, and J. Davies, *Biochim. Biophys. Acta*, **215,** 491(1970); through *Chem. Abstr.*, **73,** 118774r(1970).
(683) A. Rosen, *Biochem. Pharmacol.*, **19,** 2075(1970); through *Chem. Abstr.*, **73,** 75174a(1970).
(684) B. Roth-Schechter, G. Okita, D. Anderson, and F. Richardson, *J. Pharmacol. Exp. Ther.*, **171,** 249(1970); through *Chem. Abstr.*, **72,** 88568m(1970).

(685) A. Teitel, C. Stanescu, D. Winter, S. Sauvard, and B. Pal, *Stud. Cercet. Fiziol.*, **14,** 287(1969); through *Chem. Abstr.*, **72,** 65231g(1970).
(686) C. Van Der Vlies, *Biochem. Pharmacol.*, **19,** 859(1970); through *Chem. Abstr.*, **73,** 33586f(1970).
(687) B. Sykes, *Biochem. Biophys. Res. Commun.*, **39,** 508(1970); through *Chem. Abstr.*, **73,** 43500n(1970).
(688) S. Kim, *Soul Taehakkyo Nonmunijip, Chayon Kwahak, Uihak Kup Yahakke*, **19,** 116(1968); through *Chem. Abstr.*, **73,** 33653a(1970).
(689) D. Liegler, E. Henderson, M. Hahn, and V. Oliverio, *Clin. Pharmacol. Ther.*, **10,** 849(1969); through *Chem. Abstr.*, **72,** 30214b(1970).
(690) I. Moriguchi, S. Fushimi, and C. Ohshima, *Chem. Pharm. Bull.*, **18,** 2447(1970).
(691) N. Lakshminarayanaiah and M. White, *Physiol. Chem. Phys.*, **1,** 523(1969); through *Chem. Abstr.*, **72,** 119748b(1970).
(692) N. Laiken and G. Nemethy, *J. Phys. Chem.*, **74,** 4421 (1970).
(693) *Ibid.*, **74,** 4431(1970).
(694) W. Kuebler, G. Rau, P. Spieckermann, M. Tauchert, L. Cott, and H. Bretschneider, *Verh. Deut. Ges. Inn. Med.*, **75,** 413 (1969); through *Chem. Abstr.*, **73,** 33800w(1970).
(695) J. Krieglstein, *Klin. Wochenschr.*, **47,** 1125(1969); through *Chem. Abstr.*, **72,** 29945j(1970).
(696) G. Kivman and I. Geitman, *Vop. Med. Khim.*, **16,** 405 (1970); through *Chem. Abstr.*, **73,** 75264e(1970).
(697) N. Khanna, E. Harpur, and L. Stern, *Clin. Biochem.*, **2,** 349(1969); through *Chem. Abstr.*, **73,** 33609r(1970).
(698) E. Illes, *Acta Vet. (Budapest)*, **20,** 13(1970); through *Chem. Abstr.*, **73,** 86053m(1970).
(699) K. Brown-Grant, R. Brennan, and F. Yates, *J. Clin. Endocrinol.*, **30,** 733(1970).
(700) O. Borga, B. Hamberger, T. Malmfors, and F. Sjoqvist, *Clin. Pharmacol. Ther.*, **11,** 581(1970).
(701) S. Hamada, T. Nakagawa, T. Mori, and K. Torizuka, *J. Clin. Endocrinol.*, **31,** 166(1970).
(702) R. Bluestone, I. Kippen, J. Klinenberg, and M. Whitehouse, *J. Lab. Clin. Med.*, **76,** 85(1970); through *Chem. Abstr.*, **73,** 75242w(1970).
(703) R. Bluestone, I. Kippen, and J. Klinenberg, *Brit. Med. J.*, **4,** 590(1969); through *Chem. Abstr.*, **72,** 20501d(1970).
(704) J. Gomi, T. Aoyagi, M. Oana, Y. Mitsuno, T. Kawai, Y. Yamada, and Y. Yamada, *Nippon Kagaku Ryohogakukai Zasshi*, **17,** 1363(1969); through *Chem. Abstr.*, **72,** 77145v(1970).
(705) H. Glasser and J. Krieglstein, *Naunyn-Schmiedebergs Arch. Pharmakol.*, **265,** 321(1970); through *Chem. Abstr.*, **73,** 23664r(1970).
(706) G. Franksson and E. Anggard, *Acta Pharmacol. Toxicol.*, **28,** 209(1970); through *Chem. Abstr.*, **73,** 23652k(1970).
(707) C. Fitch, *Science*, **169,** 289(1970); through *Chem. Abstr.*, **73,** 75259g(1970).
(708) S. Curry, *J. Pharm. Pharmacol.*, **22,** 753(1970).
(709) P. Dawkins, J. McArthur, and M. Smith, *ibid.*, **22,** 405(1970).
(710) G. Curci, A. Ninni, and V. Fabbrocini, *Riforma Med.*, **84,** 197(1970); through *Chem. Abstr.*, **73,** 43431r(1970).
(711) C. Chignell, *Mol. Pharmacol.*, **6,** 1(1970); through *Chem. Abstr.*, **72,** 77096e(1970).
(712) F. Uy, D. Zubas-Adams, and F. Given, *Curr. Ther. Res., Clin. Exp.*, **12,** 306(1970); through *Chem. Abstr.*, **73,** 23683w(1970).
(713) K. James and R. Leach, *J. Pharm. Pharmacol.*, **22,** 612 (1970).
(714) K. Kakemi, H. Sezaki, T. Mitsunaga, and M. Nakano, *J. Pharm. Sci.*, **59,** 1597(1970).
(715) J. Cohen and K. Connors, *ibid.*, **59,** 1271(1970).
(716) M. Zoglio and H. Maulding, *ibid.*, **59,** 215(1970).
(717) H. Maulding and M. Zoglio, *ibid.*, **59,** 384(1970).
(718) M. Zoglio and H. Maulding, *ibid.*, **59,** 1836(1970).
(719) H. Maulding and M. Zoglio, *ibid.*, **59,** 1673(1970).
(720) J. Nagwekar and H. Kostenbauder, *ibid.*, **59,** 751(1970).
(721) I. Pitman and M. Ziser, *ibid.*, **59,** 1295(1970).
(722) T. Higuchi and H. Kristiansen, *ibid.*, **59,** 1601(1970).
(723) H. Kristiansen, M. Nakano, N. I. Nakano, and T. Higuchi, *ibid.*, **59,** 1103(1970).
(724) H. Schott, *ibid.*, **59,** 1492(1970).
(725) W.-H. Wu, T.-F. Chin, and J. L. Lach, *ibid.*, **59,** 1234(1970).
(726) *Ibid.*, **59,** 1122(1970).
(727) M. Meyer and D. Guttman, *J. Pharm. Sci.*, **59,** 33(1970).
(728) K. Shima, K. Mizojiri, and R. Yamamoto, *Yakugaku Zasshi*, **90,** 469(1970).
(729) K. Shima, S. Ichihashi, and R. Yamamoto, *ibid.*, **90,** 730(1970).
(730) K. Shima, K. Mizojiri, S. Ichihashi, and R. Yamamoto, *ibid.*, **90,** 774(1970).
(731) K. James and P. Noyce, *J. Pharm. Pharmacol.*, **22,** 109S (1970).
(732) Y. Kidani, M. Matsuo, and H. Koike, *Yakugaku Zasshi*, **90,** 452(1970).
(733) G. Hirata, *ibid.*, **90,** 359(1970).
(734) N. Tanaka, G. Hirata, and I. Utsumi, *Chem. Pharm. Bull.*, **18,** 1083(1970).
(735) E. DeRitter, L. Magid, M. Osadca, and S. Rubin, *J. Pharm. Sci.*, **59,** 229(1970).
(736) J. McCallister, T.-F. Chin, and J. Lach, *ibid.*, **59,** 1286 (1970).
(737) J. Lach and L. Bighley, *ibid.*, **59,** 1261(1970).
(738) M. Nakano and N. Patel, *ibid.*, **59,** 77(1970).
(739) T. Okano, H. Matsumoto, A. Isobe, and Y. Iwamoto, *Yakugaku Zasshi*, **90,** 1032(1970).
(740) T. Okano, H. Matsumoto, S. Ishii, and A. Isobe, *ibid.*, **90,** 716(1970).
(741) S. Borodkin and M. Yunker, *J. Pharm. Sci.*, **59,** 481(1970).
(742) E. Garrett and D. Weber, *ibid.*, **59,** 1383(1970).
(743) K. Hisatsune, *Yakugaku Zasshi*, **90,** 1212(1970).
(744) S. Horin and H. Arai, *J. Colloid Interface Sci.*, **32,** 547 (1970).
(745) E. Ullman, K. Thoma, and O. Fickel, *Arch. Pharm. (Weinhein)*, **303,** 305(1970); through *Chem. Abstr.*, **73,** 28844j(1970).
(746) M. Kassem and A. El-Nimr, *Sci. Pharm.*, **38,** 150(1970); through *Chem. Abstr.*, **73,** 123478b(1970).
(747) S. Leucuta and J. Schwartz, *Ann. Pharm. Fr.*, **28,** 283 (1970); through *Chem. Abstr.*, **73,** 123480w(1970).
(748) K. Lewis and C. Robinson, *J. Colloid Interface Sci.*, **32,** 539(1970).
(749) B. Lindman and P. Ekwall, *Kolloid-Z. Z. Polym.*, **234,** 1115(1969); through *Chem. Abstr.*, **72,** 22804d(1970).
(750) V. Malakhova, *Farmatsiya (Moscow)*, **19,** 54(1970); through *Chem. Abstr.*, **73,** 133957w(1970).
(751) R. Minder, H. Weder, and M. Bickel, *Biochem. Pharmacol.*, **19,** 2179(1970); through *Chem. Abstr.*, **73,** 86041f(1970).
(752) H. Miller and S. Friberg, *J. Colloid Interface Sci.*, **32,** 132(1970).
(753) M. Ohnishi and D. Urry, *Science*, **168,** 1091(1970).
(754) R. Quintana and A. Lasslo, *J. Colloid Interface Sci.*, **33,** 54(1970).
(755) L. Sorin, *Farmacia (Bucharest)*, **18,** 475(1970); through *Chem. Abstr.*, **73,** 133959y(1970).
(756) G. Starobinets and D. Peshko, *Vestsi Akad. Navuk Belarus. SSR, Ser. Khim. Navuk*, **1969,** 21; through *Chem. Abstr.*, **72,** 59021x(1970).
(757) W. Stumm, C. Huang, and S. Jenkins, *Croat. Chem. Acta*, **42,** 223(1970); through *Chem. Abstr.*, **73,** 80874h(1970).
(758) A. Yokoyama, H. Sakurai, and H. Tanaka, *Chem. Pharm. Bull.*, **18,** 1021(1970).
(759) J. Bunting and K. Thong, *Can. J. Chem.*, **48,** 1654(1970).
(760) D. Eagland and F. Franks, *Chem. Phys. Appl. Surface Active Subst., Proc. Int. Congr., 4th*, **2,** 535(1964); through *Chem. Abstr.*, **72,** 25177n(1970).
(761) L. Kirschenbaum and K. Kustin, *J. Chem. Soc. (A)*, **1970,** 684.
(762) P. Ionescu-Stoian, E. Savopol, S. Balliu, and S. Boteanu, *Farmacia (Bucharest)*, **17,** 583(1969); through *Chem. Abstr.*, **72,** 70612m(1970).
(763) P. Ionescu-Stoian, E. Savopol, F. Mihailescu, and V. Ionica, *ibid.*, **18,** 143(1970); through *Chem. Abstr.*, **73,** 28882v (1970).
(764) K. Heckmann and R. Woodbridge, *Chem. Phys. Appl. Surface Active Subst., Proc. Int. Congr., 4th*, **2,** 519(1964); through *Chem. Abstr.*, **72,** 25315f(1970).
(765) B. Boggiano, R. Drew, and R. Hancock, *Australas. J. Pharm.*, **51,** 14(1970); through *Chem. Abstr.*, **72,** 136374u(1970).
(766) A. Glover and M. McCulloch, *Eur. J. Pharmacol.*, **11,** 163(1970); through *Chem. Abstr.*, **73,** 86264f(1970).

(767) B. Cuna, M. Santurino, and R. Cadorniga, *J. Pharm. Belg.*, **24,** 379(1969); through *Chem. Abstr.*, **72,** 82935g(1970).

(768) G. Cuisinaud, A. Cier, and M. Solal, *Ann. Pharm. Fr.*, **27,** 687(1969); through *Chem. Abstr.*, **72,** 136342g(1970).

(769) N. Choulis and C. Rhodes, *Can. J. Pharm. Sci.*, **5,** 83 (1970).

(770) M. Casamada and D. Ramon, *Rev. Real Acad. Farm. Barcelona*, **1,** 3(1970); through *Chem. Abstr.*, **73,** 38449y(1970).

(771) A. Agren, R. Elofsson, U. Meresaar, and S. Nilsson, *Acta Pharm. Suecica*, **7,** 105(1970); through *Chem. Abstr.*, **73,** 43489r(1970).

(772) J. Jatz and B. Knowles, *J. Pharm. Sci.*, **59,** 1188(1970).

(773) *Ibid.*, **59,** 1750(1970).

(774) N. Ho, A. Suzuki, and W. Higuchi, *J. Pharm. Sci.*, **59,** 1125(1970).

(775) P. Elworthy and W. Guthrie, *J. Pharm. Pharmacol.*, **22,** 114S(1970).

(776) A. Bikhazi and W. Higuchi, *J. Pharm. Sci.*, **59,** 744(1970).

(777) A. Ghanem, W. Higuchi, and A. Simonelli, *ibid.*, **59,** 232(1970).

(778) *Ibid.*, **59,** 659(1970).

(779) A. Kamel, A. Felmeister, and N. Weiner, *J. Pharm. Sci.*, **59,** 1807(1970).

(780) A. El-Shimi and V. Izmailova, *Chim. Phys. Appl. Prat. Ag. Surface, C. R. Congr. Int. Deterg., 5th*, **2,** 309(1968); through *Chem. Abstr.*, **73,** 134170w(1970).

(781) A. Watanabe and H. Tamai, *Bull. Inst. Chem. Res., Kyoto Univ.*, **47,** 283(1969); through *Chem. Abstr.*, **72,** 136704b (1970).

(782) A. Watanabe, A. Fujii, Y. Sakamori, and H. Tamai, *Nippon Kagaku Zasshi*, **90,** 880(1969); through *Chem. Abstr.*, **72,** 36078g(1970).

(783) E. Shotton, K. Wibberley, and A. Vaziri, *Chem. Phys. Appl. Surface Active Subst., Proc. Int. Congr., 4th*, **2,** 1211(1964); through *Chem. Abstr.*, **72,** 25209z(1970).

(784) K. Shinoda and M. Fujihira, *Advan. Chem. Ser.*, **79,** 198(1967); through *Chem. Abstr.*, **72,** 25205v(1970).

(785) B. Tezak, *Croat. Chem. Acta*, **42,** 81(1970); through *Chem. Abstr.*, **73,** 80843x(1970).

(786) K. Motomura and H. Sobotka, *Chem. Phys. Appl. Surface Active Subst., Proc. Int. Congr., 4th*, **2,** 959(1964); through *Chem. Abstr.*, **72,** 25192p(1970).

(787) M. Nakagaki, N. Funasaki, and M. Nishino, *Yakugaku Zasshi*, **90,** 1088(1970).

(788) J. Davies, *Chem. Phys. Appl. Surface Active Subst., Proc. Int. Congr., 4th*, **2,** 1(1964); through *Chem. Abstr.*, **72,** 25156e(1970).

(789) A. Chatterjee and D. Chattoraj, *Kolloid-Z. Z. Polym.*, **234,** 1053(1969); through *Chem. Abstr.*, **72,** 25167j(1970).

(790) M. Castillo, *Rev. Real Acad. Farm. Barcelona*, **12,** 89 (1968); through *Chem. Abstr.*, **73,** 134162v(1970).

(791) H. Nogami, T. Nagai, and N. Nambu, *Chem. Pharm. Bull.*, **18,** 1643(1970).

(792) H. Nogami, T. Nagai, and S. Wada, *ibid.*, **18,** 342(1970).

(793) *Ibid.*, **18,** 348(1970).

(794) A. Thakkar, W. Wilham, and G. Zografi, *J. Pharm. Sci.*, **59,** 1466(1970).

(795) I. Moriguchi, S. Fushimi, and N. Kaneniwa, *Chem. Pharm. Bull.*, **18,** 449(1970).

(796) *Ibid.*, **18,** 211(1970).

(797) S. Srinivasan and P. Sawyer, *J. Colloid Interface Sci.*, **32,** 456(1970).

(798) D. Mufson and W. Higuchi, *J. Pharm. Sci.*, **59,** 601(1970).

(799) M. Nakagaki, H. Kishimoto, and K. Hirano, *Yakugaku Zasshi*, **90,** 1118(1970).

(800) F. Gstirner and C. Pick, *Arch. Pharm.*, **302,** 590(1969); through *Chem. Abstr.*, **72,** 15740b(1970).

(801) T. Wakamatsu and D. Fuerstenau, *Advan. Chem. Ser.*, **79,** 161(1967); through *Chem. Abstr.*, **72,** 25178p(1970).

(802) T. Ward and F. Getzen, *Environ. Sci. Technol.*, **4,** 28(1970); through *Chem. Abstr.*, **72,** 36110m(1970).

(803) P. Somasundaran, *J. Colloid Interface Sci.*, **31,** 557(1969); through *Chem. Abstr.*, **72,** 25274s(1970).

(804) M. Tecilazic-Stevanovic and D. Delic, *Glas. Hem. Drus., Beograd.*, **33,** 523(1968); through *Chem. Abstr.*, **72,** 136747t(1970).

(805) H. White, *Cationic Surfactants*, **1970,** 311; through *Chem. Abstr.*, **72,** 123270g(1970).

(806) E. Wolska, *Zentralbl. Veterinaermed., Reihe B*, **17,** 338 (1970); through *Chem. Abstr.*, **73,** 28889c(1970).

(807) L. Wright and J. Gaylor, *Lipids*, **4,** 526(1969); through *Chem. Abstr.*, **72,** 25258q(1970).

(808) F. Wolf and S. Wurster, *Tenside*, **7,** 140(1970); through *Chem. Abstr.*, **73,** 67896x(1970).

(809) W. Zwierzykowski, *Chem. Phys. Appl. Surface Active Subst., Proc. Int. Congr., 4th*, **2,** 801(1964); through *Chem. Abstr.*, **72,** 25162d(1970).

(810) A. Zettlemoyer and F. Micale, *Croat. Chem. Acta*, **42,** 247(1970); through *Chem. Abstr.*, **73,** 80966q(1970).

(811) J. Weber, *Soil Sci. Soc. Amer., Proc.*, **34,** 401(1970); through *Chem. Abstr.*, **73,** 29273j(1970).

(812) F. Saleeb, *Kolloid-Z. Z. Polym.*, **239,** 602(1970); through *Chem. Abstr.*, **73,** 91657r(1970).

(813) G. Petre and M. Schayer, *Electrochim. Acta*, **15,** 909 (1970); through *Chem. Abstr.*, **73,** 70143e(1970).

(814) P. Rawlings and F. Schneider, *J. Chem. Phys.*, **52,** 946 (1970); through *Chem. Abstr.*, **72,** 70933s(1970).

(815) G. Gonzalez and F. MacRitchie, *J. Colloid Interface Sci.*, **32,** 55(1970).

(816) R. Ottewill, *Croat. Chem. Acta*, **42,** 389(1970); through *Chem. Abstr.*, **73,** 81001h(1970).

(817) S. Nara, Y. Yabumoto, K. Yarnaguchi, and I. Maeda, *Nippon Nogei Kagaku Kaishi*, **43,** 570(1969); through *Chem. Abstr.*, **72,** 36102k(1970).

(818) F. Lindstrom, R. Haque, and W. Coshow, *J. Phys. Chem.*, **74,** 495(1970).

(819) H. Lange, *Chem. Phys. Appl. Surface Active Subst., Proc. Int. Congr., 4th*, **2,** 497(1964); through *Chem. Abstr.*, **72,** 36072a (1970).

(820) L. Aleinikova and A. Yudin, *Izv. Vysssh. Ucheb. Zaved., Tekhnol. Legk. Prom.*, **5,** 39(1969); through *Chem. Abstr.*, **72,** 25269u(1970).

(821) M. Kabai-Faix, S. Rohrsetzer, and E. Wolfram, *Magy. Kem. Foly.*, **76,** 166(1970); through *Chem. Abstr.*, **73,** 29330a(1970).

(822) W. Hower, *Clays Clay Miner.*, **18,** 97(1970); through *Chem. Abstr.*, **73,** 123853v(1970).

(823) P. Hess, *Z. Phys. Chem. (Frankfurt am Main)*, **67,** 69 (1969); through *Chem. Abstr.*, **72,** 70945x(1970).

(824) A. Herz, R. Danner, and G. Janusonis, *Advan. Chem. Ser.*, **79,** 173(1967); through *Chem. Abstr.*, **72,** 25253j(1970).

(825) R. Hansen, *Croat. Chem. Acta*, **42,** 385(1970); through *Chem. Abstr.*, **73,** 80847b(1970).

(826) M. Ginn, *Cationic Surfactants*, **1970,** 369; through *Chem. Abstr.*, **72,** 123269p(1970).

(827) F. Getzen and T. Ward, *J. Colloid Interface Sci.*, **31,** 441(1969); through *Chem. Abstr.*, **72,** 25263n(1970).

(828) C. Gavach, *C. R. Acad. Sci., Ser. C*, **270,** 1197(1970); through *Chem. Abstr.*, **73,** 38899v(1970).

(829) W. Cutler and D. Netzel, *Chem. Phys. Appl. Surface Active Subst., Proc. Int. Congr., 4th*, **2,** 793(1964); through *Chem. Abstr.*, **72,** 25158g(1970).

(830) M. Chatelut, G. Siclet, J. Lenoir, and C. Eyraud, *Bull. Soc. Chim. Fr.*, **10,** 3387(1969); through *Chem. Abstr.*, **72,** 25252h (1970).

(831) A. Adamson, *Croat. Chem. Acta*, **42,** 369(1970); through *Chem. Abstr.*, **73,** 80849d(1970).

(832) R. Poust and V. Smolen, *J. Pharm. Sci.*, **59,** 1461(1970).

(833) M. Mezei and A. Lee, *ibid.*, **59,** 858(1970).

(834) K. Shinoda, *J. Colloid Interface Sci.*, **34,** 278(1970).

(835) K. Shinoda and H. Takeda, *ibid.*, **32,** 642(1970).

(836) C. McDonald, *Can. J. Pharm. Sci.*, **5,** 81(1970).

(837) T. Lin, *J. Soc. Cosmet. Chem.*, **21,** 365(1970).

(838) K. Konno and A. Kitahara, *Nippon Kagaku Zasshi*, **91,** 539(1970); through *Chem. Abstr.*, **73,** 111226e(1970).

(839) M. Tomizawa and T. Kondo, *Chem. Pharm. Bull.*, **18,** 2158(1970).

(840) J. Stead and H. Taylor, *Australas. J. Pharm.*, **51,** 1(1970); through *Chem. Abstr.*, **72,** 125392x(1970).

(841) F. Spingola, *Diss. Abstr. Int. B*, **30,** 3129(1970); through *Chem. Abstr.*, **73,** 36840v(1970).

(842) F. Tokiwa and K. Ohki, *Yukagaku*, **19,** 901(1970); through *Chem. Abstr.*, **73,** 132254c(1970).

(843) F. Tokiwa, *ibid.*, **19,** 195(1970); through *Chem. Abstr.*, **73,** 46935u(1970).
(844) C. Stevens, *Kirk-Othmer Encycl. Chem. Technol., 2nd Ed.*, **19,** 507(1969); through *Chem. Abstr.*, **72,** 33532q(1970).
(845) H. Saito, *Nippon Kagaku Zasshi*, **90,** 1020(1969); through *Chem. Abstr.*, **72,** 36082d(1970).
(846) C. Prakash and S. Srivastava, *Z. Phys. Chem. (Leipzig)*, **244,** 200(1970); through *Chem. Abstr.*, **73,** 134172y(1970).
(847) S. Ropuszynski and J. Perka, *Wiad. Chem.*, **24,** 257(1970); through *Chem. Abstr.*, **73,** 46936v(1970).
(848) G. Pasztor and B. Veroczey, *Kolor. Ert.*, **12,** 108(1970); through *Chem. Abstr.*, **73,** 121738n(1970).
(849) D. Napper, *J. Colloid Interface Sci.*, **32,** 106(1970); through *Chem. Abstr.*, **72,** 36176n(1970).
(850) Y. Komeda and J. Mino, *Yukagaku*, **19,** 492(1970); through *Chem. Abstr.*, **73,** 111221z(1970).
(851) K. Kaibara, T. Nakahara, I. Satake, and R. Matuura, *Mem. Fac. Sci., Kyushu Univ., Ser. C*, **7,** 1(1970); through *Chem. Abstr.*, **73,** 121735j(1970).
(852) K. Kaganskaya, T. Deikalo, and V. Ben'kovskii, *Tr. Inst. Khim. Nefti Prir. Solei, Akad. Nauk Kaz. SSR*, **1,** 251(1970); through *Chem. Abstr.*, **73,** 132255d(1970).
(853) Z. Jedrusiak, *Przegl. Wlok.*, **23,** 376(1969); through *Chem. Abstr.*, **72,** 33531p(1970).
(854) H. Hoffmann, *Seifen-Oele-Fette-Wachse*, **95,** 621(1969); through *Chem. Abstr.*, **72,** 22801a(1970).
(855) T. Hikota, *Bull. Chem. Soc. Jap.*, **43,** 2236(1970); through *Chem. Abstr.*, **73,** 100284w(1970).
(856) R. Heusch, *Kolloid-Z. Z. Polym.*, **236,** 31(1970); through *Chem. Abstr.*, **72,** 123277q(1970).
(857) G. Gantz, *Amer. Dyest. Rep.*, **57,** 885(1968); through *Chem. Abstr.*, **72,** 33530n(1970).
(858) K. Furuse, *Yukagaku*, **18,** 530(1969); through *Chem. Abstr.*, **72,** 47317k(1970).
(859) D. Bass, *Mfg. Chem. Aerosol News*, **41,** 30(1970).
(860) L. Carvalho, *Rev. Port. Farm.*, **19,** 86(1969); through *Chem. Abstr.*, **72,** 136304w(1970).
(861) J. Zatz, *J. Colloid Interface Sci.*, **33,** 465(1970).
(862) J. Bloor, J. Morrison, and C. Rhodes, *J. Pharm. Sci.*, **59,** 387(1970).
(863) C. McDonald, *J. Pharm. Pharmacol.*, **22,** 774(1970).
(864) P. Mukerjee, J. Perrin, and E. Witzke, *J. Pharm. Sci.*, **59,** 1513(1970).
(865) J. Adderson and H. Taylor, *J. Pharm. Pharmacol.*, **22,** 523(1970).
(866) J. Swarbrick and J. Daruwala, *J. Phys. Chem.*, **74,** 1293 (1970).
(867) S. Yalkowsky and G. Zografi, *J. Colloid Interface Sci.*, **34,** 525(1970).
(868) A. Florence and R. Parfitt, *J. Pharm. Pharmacol.*, **22,** 121S(1970).
(869) A. Potanin and N. Dubrovich, *Dokl. Akad. Nauk SSSR*, **188,** 849(1969); through *Chem. Abstr.*, **72,** 33536u(1970).
(870) S. Rehfeld, *J. Colloid Interface Sci.*, **34,** 518(1970).
(871) S. Ohnishi, T. Cyr, and H. Fukushima, *Bull. Chem. Soc. Jap.*, **43,** 673(1970); through *Chem. Abstr.*, **72,** 136752r(1970).
(872) S. Ohki and O. Aono, *J. Colloid Interface Sci.*, **32,** 270 (1970); through *Chem. Abstr.*, **72,** 125362n(1970).
(873) T. Nakagawa and H. Inoue, *Chem. Phys. Appl. Surface Active Subst., Proc. Int. Congr., 4th*, **2,** 569(1964); through *Chem. Abstr.*, **72,** 25360s(1970).
(874) P. Mukerjee, *J. Phys. Chem.*, **74,** 3824(1970); through *Chem. Abstr.*, **73,** 123885g(1970).
(875) P. Mijnlieff, *J. Colloid Interface Sci.*, **33,** 255(1970); through *Chem. Abstr.*, **73,** 29238b(1970).
(876) C. McDonald, *J. Pharm. Pharmacol.*, **22,** 148(1970).
(877) W. Malik, A. Jain, and O. Jhamb, *Int. J. Appl. Radiat. Isotop.*, **21,** 564(1970); through *Chem. Abstr.*, **73,** 132249e(1970).
(878) R. Little, *J. Phys. Chem.*, **74,** 1817(1970); through *Chem. Abstr.*, **72,** 134445u(1970).
(879) G. Lindblom, B. Lindman, and L. Mandell, *J. Colloid Interface Sci.*, **34,** 262(1970); through *Chem. Abstr.*, **73,** 134233u (1970).
(880) H. Kohara, N. Ishibashi, and T. Masuzaki, *Bunseki Kagaku*, **19,** 467(1970); through *Chem. Abstr.*, **73,** 134232t(1970).
(881) O. Khelevina and N. Kanyaev, *Izv. Vyssh. Ucheb. Zaved., Khim. Khim. Tekhnol.*, **13,** 1120(1970); through *Chem. Abstr.*, **73,** 132252a(1970).
(882) E. Johnson and D. Ludium, *Biochem. Pharmacol.*, **18,** 2675(1969); through *Chem. Abstr.*, **72,** 15739h(1970).
(883) R. Hudson and B. Pethica, *Chem. Phys. Appl. Surface Active Subst., Proc. Int. Congr., 4th*, **2,** 631(1964); through *Chem. Abstr.*, **72,** 22813f(1970).
(884) T. Hitoka and K. Meguro, *J. Amer. Oil Chem. Soc.*, **47,** 197(1970); through *Chem. Abstr.*, **73,** 26897c(1970).
(885) M. Hato and K. Shinoda, *Nippon Kagaku Zasshi*, **91,** 27(1970); through *Chem. Abstr.*, **73,** 16626b(1970).
(886) E. Graber and R. Zana, *Kolloid-Z. Z. Polym.*, **238,** 749 (1970); through *Chem. Abstr.*, **73,** 123876e(1970).
(887) J. Gordon, *J. Phys. Chem.*, **74**(1970); through *Chem. Abstr.*, **73,** 123884f(1970).
(888) B. Bennion and E. Eyring, *J. Colloid Interface Sci.*, **32,** 286(1970); through *Chem. Abstr.*, **72,** 70970b(1970).
(889) B. Barry, J. Morrison, and G. Russell, *ibid.*, **33,** 554(1970).
(890) J. Daruwala, *Diss. Abstr., Int. B*, **30,** 581(1969); through *Chem. Abstr.*, **73,** 29284p(1970).
(891) I. Danielsson, *Chem. Phys. Appl. Surface Active Subst., Proc. Int. Congr., 4th*, **2,** 555(1964); through *Chem. Abstr.*, **72,** 22805e(1970).
(892) J. Crokill, K. Gemmell, J. Goodman, and T. Walker, *Trans. Faraday Soc.*, **66,** 1817(1970); through *Chem. Abstr.*, **73,** 80920v(1970).
(893) H. Chung and I. Heilweil, *J. Phys. Chem.*, **74,** 488(1970).
(894) A. Chinnikova, Z. Markina, and P. Rebinder, *Kolloid. Zh.*, **32,** 288(1970); through *Chem. Abstr.*, **73,** 29289u(1970).
(895) M. Carey and D. Small, *J. Colloid Interface Sci.*, **31,** 382(1969); through *Chem. Abstr.*, **72,** 25358x(1970).
(896) J. Adderson and H. Taylor, *Chem. Phys. Appl. Surface Active Subst., Proc. Int. Congr., 4th*, **2,** 613(1964); through *Chem. Abstr.*, **72,** 25288z(1970).
(897) S. Dukhin, B. Deryagin, and N. Semenikhin, *Dokl. Akad. Nauk SSSR*, **192,** 357(1970); through *Chem. Abstr.*, **73,** 80983t (1970).
(898) J. Mizuguchi, M. Takahashi, and M. Aizawa, *Nippon Kagaku Zasshi*, **91,** 723(1970); through *Chem. Abstr.*, **73,** 134231s (1970).
(899) R. Ottewill, *Annu. Rep. Progr. Chem., Sect. A*, **66,** 183 (1969); through *Chem. Abstr.*, **73,** 123809k(1970).
(900) R. Ottewill, *Croat. Chem. Acta*, **42,** 395(1970); through *Chem. Abstr.*, **73,** 80845z(1970).
(901) J. Pouradier, *J. Chim. Phys. Physicochim. Biol.*, **67,** 229(1970); through *Chem. Abstr.*, **73,** 29327e(1970).
(902) D. Woessner, B. Snowden, and Y. Chiu, *J. Colloid Interace Sci.*, **34,** 283(1970); through *Chem. Abstr.*, **73,** 134235w(1970).
(903) J. Visser, *Rep. Progr. Appl. Chem.*, **53,** 714(1968); through *Chem. Abstr.*, **72,** 36057z(1970).
(904) M. Gara and G. Szatlmayer, *Kolor. Ert.*, **12,** 53(1970); through *Chem. Abstr.*, **73,** 67894v(1970).
(905) P. Joos, *Chem. Phys. Appl. Surface Active Subst., Proc. Int. Congr., 4th*, **2,** 1161(1964); through *Chem. Abstr.*, **72,** 25367z (1970).
(906) E. Rubin and J. Jorne, *J. Colloid Interface Sci.*, **33,** 208 (1970); through *Chem. Abstr.*, **73,** 38861b(1970).
(907) D. Okun and J. Baars, *Chem. Phys. Appl. Surface Active Subst., Proc. Int. Congr., 4th*, **2,** 1179(1964); through *Chem. Abstr.*, **72,** 25166h(1970).
(908) J. Zatz, N. Weiner, and M. Gibaldi, *J. Colloid Interface Sci.*, **33,** 1(1970).
(909) L. Nagy and G. Schay, *Magy. Kem. Lapia*, **25,** 439(1970); through *Chem. Abstr.*, **73,** 123858a(1970).
(910) M. Ginn, S. Dunn, and E. Jungermann, *J. Amer. Oil Chem. Soc.*, **47,** 83(1970); through *Chem. Abstr.*, **72,** 119985b(1970).
(911) F. Greenwood, G. Parfitt, N. Picton, and D. Wharton, *Advan. Chem. Ser.*, **79,** 135(1967); through *Chem. Abstr.*, **72,** 25254k(1970).
(912) A. Kassem and S. Bayoumy, *Bull. Fac. Pharm., Cairo Univ.*, **8,** 181(1969); through *Chem. Abstr.*, **73,** 69808u(1970).
(913) J. Padday, *Chem. Phys. Appl. Surface Active Subst., Proc. Int. Congr., 4th*, **2,** 299(1964); through *Chem. Abstr.*, **72,** 25250f (1970).
(914) T. Tsunoda, *Yukagaku*, **18,** 839(1969); through *Chem. Abstr.*, **72,** 70896g(1970).
(915) G. Zografi and M. Munshi, *J. Pharm. Sci.*, **59,** 819(1970).

(916) S. Goerlich, *Chem. Phys. Appl. Surface Active Subst., Proc. Int. Congr., 4th*, **2**, 51(1964); through *Chem. Abstr.*, **72**, 25204u(1970).
(917) B. Kamienski, J. Krul, T. Mlodnicka, and J. Pawlikowska-Czubak, *ibid.*, **2**, 225(1964); through *Chem. Abstr.*, **72**, 25200q (1970).
(918) W. Marple, *ibid.*, **3**, 59(1964); through *Chem. Abstr.*, **72**, 25194n(1970).
(919) F. Neuwald and K. Fetting, *ibid.*, **3**, 351(1964); through *Chem. Abstr.*, **72**, 24582d(1970).
(920) J. Myszkowski, A. Zielinski, E. Milchert, and S. Ptaszynska, *Roz. Chem.*, **44**, 1283(1970); through *Chem. Abstr.*, **73**, 134166z (1970).
(921) G. Bell, S. Levine, and L. McCartney, *J. Colloid Interface Sci.*, **33**, 335(1970); through *Chem. Abstr.*, **73**, 38973q(1970).
(922) S. Levine, *Croat. Chem. Acta*, **42**, 377(1970); through *Chem. Abstr.*, **73**, 80848c(1970).
(923) C. Miller and L. Scriven, *J. Colloid Interface Sci.*, **33**, 361 (1970); through *Chem. Abstr.*, **73**, 38868j(1970).
(924) *Ibid.*, **33**, 372(1970); through *Chem. Abstr.*, **73**, 38869k (1970).
(925) F. Saleeb and J. Kitchener, *Chem. Phys. Appl. Surface Active Subst., Proc. Int. Congr., 4th*, **2**, 129(1964); through *Chem. Abstr.*, **72**, 25203t(1970).
(926) S. Mehta, P. Bernardo, W. Higuchi, and A. Simonelli, *J. Pharm. Sci.*, **59**, 638(1970).
(927) A. Simonelli, S. Mehta, and W. Higuchi, *ibid.*, **59**, 633 (1970).
(928) B. Craven and G. Gartland, *ibid.*, **59**, 1666(1970).
(929) K. Ito, *Chem. Pharm. Bull.*, **18**, 1519(1970).
(930) *Ibid.*, **18**, 1509(1970).
(931) R. Tawashi and J. Piccolo, *Pharm. Acta Helv.*, **45**, 653 (1970); through *Chem. Abstr.*, **73**, 123447r(1970).
(932) S. Davis, B. Warburton, and J. Dippy, *J. Pharm. Sci.*, **59**, 1764(1970).
(933) B. Barry and A. Grace, *J. Pharm. Pharmacol.*, **22**, 147S (1970).
(934) B. Barry and G. Saunders, *ibid.*, **22**, 139S(1970).
(935) L. Block and P. Lamy, *J. Soc. Cosmet. Chem.*, **21**, 645 (1970).
(936) S. Chien, S. Usami, R. Dellenback, and M. Gregersen, *Amer. J. Physiol.*, **219**, 143(1970).
(937) J. Polon, *J. Soc. Cosmet. Chem.*, **21**, 347(1970).
(938) R. Calcinari, *Farmaco, Ed. Prat.*, **25**, 403(1970); through *Chem. Abstr.*, **73**, 69755z(1970).
(939) S. Davis, *Amer. Perfum. Cosmet.*, **85**, 45(1970).
(940) G. Bashura, A. Lekhan, and I. Kovalev, *Farm. Zh. (Kiev)*, **25**, 34(1970); through *Chem. Abstr.*, **73**, 80469e(1970).
(941) G. Bashura, M. Gluzman, and E. Labunskii, *ibid.*, **25**, 56(1970); through *Chem. Abstr.*, **73**, 28885y(1970).
(942) F. Gstirner and R. Meisenberg, *Arch. Pharm. (Weinheim)*, **303**, 872(1970); through *Chem. Abstr.*, **73**, 133948u(1970).
(943) K. Khristov, *Farmacia*, **17**, 331(1969); through *Chem. Abstr.*, **72**, 24581c(1970).
(944) M. Kassem and A. Mattha, *Pharm. Acta Helv.*, **45**, 355(1970); through *Chem. Abstr.*, **73**, 48521e(1970).
(945) *Ibid.*, **45**, 345(1970); through *Chem. Abstr.*, **73**, 48520d (1970).
(946) J. Linares, F. Huertas, and E. Barahona, *Bol. Soc. Espan. Ceram.*, **8**, 635(1969); through *Chem. Abstr.*, **73**, 70170m(1970).
(947) S. Onogi and T. Matsumoto, *Shikizai Kyokaishi*, **43**, 389(1970); through *Chem. Abstr.*, **73**, 123814h(1970).
(948) C. Parkinson, S. Matsumoto, and P. Sherman, *J. Colloid Interface Sci.*, **33**, 150(1970); through *Chem. Abstr.*, **72**, 136812k (1970).
(949) A. Rutkowski and Z. Elsner, *Fette, Seifen, Anstrichm.*, **71**, 1015(1969); through *Chem. Abstr.*, **72**, 70610j(1970).
(950) M. Watase and K. Arakawa, *Nippon Kagaku Zasshi*, **90**, 996(1969); through *Chem. Abstr.*, **72**, 25354t(1970).
(951) M. Watase, *Nippon Shokuhin Kogyo Gakkai-Shi*, **17**, 148(1970); through *Chem. Abstr.*, **73**, 80985v(1970).
(952) M. Watase and K. Arakawa, *Nippon Kagaku Zasshi*, **91**, 324(1970); through *Chem. Abstr.*, **73**, 38965p(1970).
(953) M. Watase, *Nippon Shokuhin Kogyo Gakkai-Shi*, **17**, 252(1970); through *Chem. Abstr.*, **73**, 80984u(1970).
(954) J. Smith, *J. Soc. Cosmet. Chem.*, **21**, 541(1970).
(955) Y. Fujiyama, S. Tahara, and Y. Yumano, *ibid.*, **21**, 625 (1970).
(956) J. Poole, *J. Pharm. Sci.*, **59**, 1255(1970).
(957) J. Perrin and J. Vallner, *J. Pharm. Pharmacol.*, **22**, 758 (1970).
(958) J. Mielck and E. Garrett, *J. Pharm. Sci.*, **59**, 760(1970).
(959) J. Kirschbaum, W. Slusarchyk, and F. Weisenborn, *ibid.*, **59**, 749(1970).
(960) P. Laskar and R. Mrtek, *ibid.*, **59**, 1727(1970).
(961) S. Kaplan, *ibid.*, **59**, 309(1970).
(962) H. Newmark and J. Berger, *ibid.*, **59**, 1246(1970).
(963) H. Newmark, J. Berger, and J. Carstensen, *ibid.*, **59**, 1249(1970).
(964) J. Kirschbaum, A. Aszalos, F. Weisenborn, and N. Coy, *J. Colloid Interface Sci.*, **33**, 439(1970).
(965) A. Shalita and V. Wheatley, *J. Invest. Dermatol.*, **54**, 413(1970).
(966) O. Kitamoto, K. Fukaya, and G. Tomori, *Nippon Kagaku Ryohogakukai Zasshi*, **17**, 1934(1969); through *Chem. Abstr.*, **72**, 98982f(1970).
(967) D. Popova, *Farmatsiya (Sofia)*, **20**, 24(1970); through *Chem. Abstr.*, **73**, 38502k(1970).
(968) F. Caruntu, C. Bocarnea, and S. Filipescu, *Viata Med.*, **16**, 1469(1969); through *Chem. Abstr.*, **72**, 130695c(1970).
(969) V. Balutsov, *Farmatsiya (Sofia)*, **20**, 34(1970); through *Chem. Abstr.*, **73**, 38500h(1970).
(970) S. Boteanu, S. Balliu-Mutu, E. Aiteanu, and O. Ludu, *Farmacia*, **17**, 681(1969); through *Chem. Abstr.*, **72**, 103672m(1970).
(971) S. Boteanu, S. Balliu-Mutu, and M. Medianu, *ibid.*, **17**, 689(1969); through *Chem. Abstr.*, **72**, 103679u(1970).
(972) T. Iwasaki, *Osaka Shiritsu Daigaku Igaku Zasshi*, **18**, 177(1969); through *Chem. Abstr.*, **72**, 29980s(1970).
(973) T. Kainuma, *Niigata Igakkai Zasshi*, **84**, 42(1970); through *Chem. Abstr.*, **73**, 2291b(1970).
(974) S. Kinsky, *Annu. Rev. Pharmacol.*, **10**, 119(1970); through *Chem. Abstr.*, **73**, 12692x(1970).
(975) V. Majkus, A. Horakova, F. Vymola, and M. Stol, *J. Biomed. Mater. Res.*, **3**, 443(1969); through *Chem. Abstr.*, **72**, 30133z(1970).
(976) W. Marget and F. Daschner, *Arzneim.-Forsch.*, **19**, 1956 (1969); through *Chem. Abstr.*, **72**, 53630y(1970).
(977) Z. Modr, K. Dvoracek, and A. Necaskova, *Rev. Czech. Med.*, **16**, 84(1970); through *Chem. Abstr.*, **73**, 108160y(1970).
(978) H. Nerlo and S. Umer, *Acta Pol. Pharm.*, **27**, 135(1970); through *Chem. Abstr.*, **73**, 80443s(1970).
(979) G. Renzini, L. Ravagnan, and P. Ricci, *Antibiotica*, **6**, 309(1968); through *Chem. Abstr.*, **72**, 119777k(1970).
(980) Y. Ueda, *Jap. J. Antibiot.*, **23**, 48(1970); through *Chem. Abstr.*, **73**, 119099m(1970).
(981) K. Price, *Advan. Appl. Microbiol.*, **11**, 17(1969); through *Chem. Abstr.*, **72**, 136305x(1970).
(982) D. Popova, *Farmatsiya (Sofia)*, **19**, 26(1969); through *Chem. Abstr.*, **72**, 35735g(1970).
(983) G. Schneller, *Amer. J. Hosp. Pharm.*, **27**, 485(1970).
(984) A. Suzuki, W. Higuchi, and N. Ho, *J. Pharm. Sci.*, **59**, 644(1970).
(985) *Ibid.*, **59**, 651(1970).
(986) M. Rowland, L. Benet, and S. Riegelman, *J. Pharm. Sci.*, **59**, 364(1970).
(987) C. Evert and M. Randall, *ibid.*, **59**, 403(1970).
(988) S. Kaplan, M. Lewis, M. Schwartz, E. Postma, S. Cotler, C. Abruzzo, T. Lee, and R. Weinfeld, *ibid.*, **59**, 1569(1970).
(989) K. Bischoff, R. Dedrick, and D. Zaharko, *ibid.*, **59**, 149(1970).
(990) J. Loo and S. Riegelman, *ibid.*, **59**, 53(1970).
(991) J. Robertson and O. Bode, *J. Pharm. Pharmacol.*, **22**, 423(1970).
(992) H. Nogami, T. Nagai, and T. Sonobe, *Chem. Pharm. Bull.*, **18**, 2101(1970).
(993) T. Bates, J. Galownia, and W. Johns, *ibid.*, **18**, 656(1970).
(994) F. Mueller and S. Lieberman, *J. Pharm. Sci.*, **59**, 514 (1970).
(995) S. Cucinell and W. Perl, *ibid.*, **59**, 1423(1970).
(996) H. Stricker, *Pharm. Ind.*, **31**, 794(1969); through *Chem. Abstr.*, **72**, 88590n(1970).
(997) J. Wagner, *Drug Intel. Clin. Pharm.*, **4**, 190(1970); through *Chem. Abstr.*, **73**, 97328f(1970).

(998) M. Van Oudtshoorn and F. Potgieter, *Pharm. Weekbl.*, **105,** 409(1970); through *Chem. Abstr.*, **73,** 7168b(1970).
(999) W. Zeman and S. Symchowicz, *Amer. J. Vet. Res.*, **31,** 1293(1970); through *Chem. Abstr.*, **73,** 86036h(1970).
(1000) M. Boucard, J. Serrano, J. Giroux, and A. Panis, *Trav. Soc. Pharm. Montpellier*, **30,** 143(1970); through *Chem. Abstr.*, **73,** 101998u(1970).
(1001) J. Raaflaub, *Experientia*, **26,** 457(1970); through *Chem. Abstr.*, **73,** 28854n(1970).
(1002) B. Murty and R. Baxter, *Indian J. Pharm.*, **32,** 51(1970); through *Chem. Abstr.*, **73,** 54134x(1970).
(1003) K. Bischoff and R. Dedrick, *J. Theoret. Biol.*, **29,** 63(1970); through *Chem. Abstr.*, **73,** 129505e(1970).
(1004) E. Gladtke and H. Von Hattingberg, *Z. Kinderheilk.*, **108,** 201(1970); through *Chem. Abstr.*, **73,** 97028h(1970).
(1005) M. Bickel, *Present Status Psychotropic Drugs, Proc. Int. Congr. Coll. Int. Neuro-Psychopharmacol., 6th*, **1968,** 68; through *Chem. Abstr.*, **72,** 65198b(1970).
(1006) M. Gibaldi, *Develop. Saf. More Eff. Drugs, Symp.*, **1967,** 81; through *Chem. Abstr.*, **72,** 1822t(1970).
(1007) F. Dost, *Deut. Med. Wochenschr.*, **95,** 1713(1970); through *Chem. Abstr.*, **73,** 118718a(1970).
(1008) W. Fuerst and M. Falk, *Pharmazie*, **25,** 205(1970); through *Chem. Abstr.*, **73,** 118701q(1970).
(1009) O. Araujo and E. Garrett, *Annu. Rep. Med. Chem.*, **1968,** 302; through *Chem. Abstr.*, **73,** 7107f(1970).
(1010) W. Purcell and J. Clayton, *ibid.*, **1968,** 314; through *Chem. Abstr.*, **72,** 119628n(1970).
(1011) A. Clarke, J. Presser, and M. Denborough, *J. Pharm. Pharmacol.*, **22,** 853(1970).
(1012) A. Silvers, J. Farguhar, R. Lerner, and G. Reaven, *J. Lab. Clin. Med.*, **75,** 175(1970).
(1013) A. Cammarata, R. Allen, J. Seydel, and E. Wempe, *J. Pharm. Sci.*, **59,** 1496(1970).
(1014) Y. Martin, *J. Med. Chem.*, **13,** 145(1970).
(1015) A. Cammarata and S. Yau, *ibid.*, **13,** 93(1970).
(1016) T. Higuchi and S. Davis, *J. Pharm. Sci.*, **59,** 1376(1970).
(1017) M. Yamazaki, N. Kakeya, T. Morishita, A. Kamada, and M. Aoki, *Chem. Pharm. Bull.*, **18,** 702(1970).
(1018) N. Kakeya, N. Yata, A. Kamada, and M. Aoki, *ibid.*, **18,** 191(1970).
(1019) F. Plakogiannis, E. Lien, C. Harris, and J. Biles, *J. Pharm. Sci.*, **59,** 197(1970).
(1020) D. Yung, M. Vohra, and I. Chu, *ibid.*, **59,** 1405(1970).
(1021) R. Feldmann and H. Maibach, *J. Invest. Dermatol.*, **54,** 399(1970).
(1022) G. Biagi, M. Guerra, A. Barbaro, and M. Gamba, *J. Med. Chem.*, **13,** 511(1970).
(1023) M. Yamazaki, N. Kakeya, T. Morishita, A. Kamada, and M. Aoki, *Chem. Pharm. Bull.*, **18,** 708(1970).
(1024) T. Vecchio, *J. Clin. Pharmacol. J. New Drugs*, **10,** 382 (1970).
(1025) M. Cahn and E. Levy, *Hospital (Rio de Janeiro)*, **76,** 227(1969); through *Chem. Abstr.*, **72,** 53647j(1970).
(1026) H. Keberle, W. Reiss, H. Meyer-Brunot, and K. Schmid, *Present Status Psychotropic Drugs, Proc. Int. Congr. Coll. Int. Neuro-Psychopharmacol., 6th*, **1968,** 123; through *Chem. Abstr.*, **73,** 118746h(1970).
(1027) E. Renier, J. Boissier, and A. Renier-Cornec, *Arch. Int. Pharmacodyn. Ther.*, **186,** 18(1970); through *Chem. Abstr.*, **73,** 118851p(1970).
(1028) G. Cloutier, G. Goyer, R. Bolduc, and R. Salvador, *ibid.*, **184,** 75(1970); through *Chem. Abstr.*, **72,** 130698f(1970).
(1029) E. Saias, A. Jodet, and J. Philippe, *Ann. Pharm. Fr.*, **27,** 557(1969); through *Chem. Abstr.*, **72,** 125018e(1970).
(1030) S. Snyder and E. Richelson, *Psychotomimetic Drugs, Proc. Workshop*, **1969,** 43; through *Chem. Abstr.*, **73,** 118762k (1970).
(1031) J. Puetter and G. Gehrmann, *Klin. Wochenschr.*, **47,** 1324 (1969); through *Chem. Abstr.*, **72,** 65290a(1970).
(1032) E. Schroeder, R. Albrecht, and C. Rufer, *Arzneim.-Forsch.* **20,** 737(1970); through *Chem. Abstr.*, **73,** 75210j(1970).
(1033) G. Ciaffi and P. Ricci, *Gazz. Int. Med. Chir.*, **73,** 4987 (1968); through *Chem. Abstr.*, **73,** 43420m(1970).
(1034) S. Szinai, *Pharma Int.*, **6,** 227(1969); through *Chem. Abstr.*, **72,** 130667v(1970).
(1035) E. Ariens, *Pure Appl. Chem.*, **19,** 187(1969); through *Chem. Abstr.*, **72,** 119655u(1970).
(1036) S. Davis, *Experientia*, **26,** 671(1970); through *Chem. Abstr.*, **73,** 75587n(1970).
(1037) S. Kang and J. Green, *Nature (London)*, **226,** 645(1970); through *Chem. Abstr.*, **73,** 23663q(1970).
(1038) B. Ho, V. Estevez, and W. McIsaac, *J. Pharm. Sci.*, **59,** 1780(1970).
(1039) L. Prescott, R. Steel, and W. Ferrier, *Clin. Pharmacol. Ther.*, **11,** 496(1970).
(1040) S. Feldman, M. Salvino, and M. Gibaldi, *J. Pharm. Sci.*, **59,** 705(1970).
(1041) W. Davis, R. Pfeiffer, and J. Quay, *ibid.*, **59,** 960(1970).
(1042) G. Levy and A. Perala, *ibid.*, **59,** 874(1970).
(1043) A. Florence, *J. Pharm. Pharmacol.*, **22,** 265(1970).
(1044) W. Lowenthal, J. Borzelleca, and C. Corder, Jr., *J. Pharm. Sci.*, **59,** 1353(1970).
(1045) W. Chiou and S. Riegelman, *ibid.*, **59,** 937(1970).
(1046) P. Jablon, G. Banker, and V. Smolen, *ibid.*, **59,** 1143 (1970).
(1047) E. Wang and E. Hammarlund, *ibid.*, **59,** 1559(1970).
(1048) H. Jun and E. Triggs, *ibid.*, **59,** 306(1970).
(1049) M. Gibaldi and S. Feldman, *ibid.*, **59,** 579(1970).
(1050) A. Cooke and J. Hunt, *Amer. J. Dig. Dis.*, **15,** 95(1970); through *Chem. Abstr.*, **72,** 130689d(1970).
(1051) G. Embery and P. Dugard, *Brit. J. Dermatol., Suppl.*, **81,** 63(1969); through *Chem. Abstr.*, **72,** 103686u(1970).
(1052) M. Gibaldi, *Fed. Proc., Fed. Amer. Soc. Exp. Biol.*, **29,** 1343(1970); through *Chem. Abstr.*, **73,** 86025d(1970).
(1053) R. Borodkina, *Tr. 1 [Pervogo] Mosk. Med. Inst.*, **61,** 119(1968); through *Chem. Abstr.*, **72,** 47338t(1970).
(1054) J. Kucera, B. Fecak, and M. Mandak, *Cesk. Farm.*, **19,** 60(1970); through *Chem. Abstr.*, **73,** 59283e(1970).
(1055) R. Kato, A. Tankanaka, K. Onoda, and Y. Omori, *Jap. J. Pharmacol.*, **19,** 331(1969); through *Chem. Abstr.*, **72,** 1854e(1970).
(1056) D. Munro, *Brit. J. Dermatol., Suppl.*, **81,** 92(1969); through *Chem. Abstr.*, **72,** 103688w(1970).
(1057) A. Popovici and M. Ionescu, *Farmacia (Bucharest)*, **18,** 545(1970); through *Chem. Abstr.*, **73,** 133973y(1970).
(1058) T. Sweeney and D. Downing, *J. Invest. Dermatol.*, **55,** 135(1970).
(1059) W. Oliver, S. Shaw, and J. Christian, *Radiochem. Radioanal. Lett.*, **2,** 279(1969); through *Chem. Abstr.*, **72,** 119929m(1970).
(1060) E. Ragazzi and G. Veronese, *Atti Ist. Veneto Sci., Lett. Arti, Cl. Sci. Mat. Natur.*, **126,** 1(1968); through *Chem. Abstr.*, **72,** 47345t(1970).
(1061) R. Scheuplein and L. Ross, *J. Soc. Cosmet. Chem.*, **21,** 853(1970).
(1062) P. Armstrong, J. Carless, and R. Enever, *J. Mond. Pharm.*, **13,** 513(1970); through *Chem. Abstr.*, **73,** 59284f(1970).
(1063) E. Delacoux, M. Pagniez, T. Gousson, and N. Cesbron, *Therapie*, **25,** 553(1970); through *Chem. Abstr.*, **73,** 33840j(1970).
(1064) L. Diamond, *Arch. Int. Pharmacodyn. Ther.*, **185,** 246 (1970); through *Chem. Abstr.*, **73,** 64541s(1970).
(1065) P. Febvre, J. Aiache, and J. Bex, *C. R. Soc. Biol.*, **163,** 1160(1969); through *Chem. Abstr.*, **72,** 130681v(1970).
(1066) A. Flora, *Curr. Ther. Res., Clin. Exp.*, **12,** 661(1970); through *Chem. Abstr.*, **73,** 129472s(1970).
(1067) Z. Hanko, Z. Csath, I. Csegedi, I. Papp, L. Adam, E. Szantho, E. Peteanu, M. Gaspar, and L. Domokos, *Farmacia (Bucharest)*, **17,** 705(1969); through *Chem. Abstr.*, **72,** 136365s(1970).
(1068) R. Helmi, A. Elian, M. Mustafa, H. El-Sayed, and S. El-Razeky, *J. Egypt. Med. Ass.*, **52,** 392(1969); through *Chem. Abstr.*, **73,** 75192e(1970).
(1069) K. Marshall, *Cron. Chim.*, **23,** 19(1969); through *Chem. Abstr.*, **72,** 82918d(1970).
(1070) G. Zoni and G. Bulletti, *Boll. Chim. Farm.*, **108,** 426 (1969); through *Chem. Abstr.*, **72,** 30204y(1970).
(1071) S. Ljungbers and G. Otto, *Acta Pharm. Suecica*, **7,** 449(1970); through *Chem. Abstr.*, **73,** 112920p(1970).
(1072) K. Muenzel, *Cron. Farm.*, **13,** 74(1970); through *Chem. Abstr.*, **73,** 59285g(1970).
(1073) W. Reetz and P. Speiser, *Pharm. Acta Helv.*, **45,** 461(1970); through *Chem. Abstr.*, **73,** 80461w(1970).
(1074) W. Ritschel, *Oesterr. Apoth. Ztg.*, **24,** 21(1970); through *Chem. Abstr.*, **72,** 119643p(1970).

(1075) I. Setnikar, *Boll. Chim. Farm.*, **108,** 529(1969); through *Chem. Abstr.*, **72,** 125017d(1970).
(1076) M. Sugiura, T. Ogiso, T. Sakai, and C. Watabe, *Gifu Yakka Daigaku Kiyo*, **18,** 54(1968); through *Chem. Abstr.*, **72,** 47339u(1970).
(1077) C. Woo, S. Kim, and M. Lee, *Soul Taehakkyo Nonmunijip, Chayon Kwahak, Uihak Kup Yahakke*, **18,** 78(1967); through *Chem. Abstr.*, **73,** 33789z(1970).
(1078) M. Mattila, H. Iddanpaan, and S. Takki, *Farm. Aikak.*, **77,** 205(1968); through *Chem. Abstr.*, **72,** 30222c(1970).
(1079) A. Viala and J. Cano, *Therapie*, **24,** 1115(1969); through *Chem. Abstr.*, **72,** 88519w(1970).
(1080) P. Kabasakalian, M. Katz, B. Rosenkrantz, and E. Townley, *J. Pharm. Sci.*, **59,** 595(1970).
(1081) W. Jusko, G. Levy, S. Yaffe, and R. Gorodischer, *ibid.*, **59,** 473(1970).
(1082) G. Levy, R. O'Reilly, P. Aggeler, and G. Keech, *Clin. Pharmacol. Ther.*, **11,** 372(1970).
(1083) K. Morisaka and Y. Nakamoto, *Yakugaku Zasshi*, **90,** 634(1970).
(1084) T. Nadai, K. Nishii, and A. Tatematsu, *ibid.*, **90,** 262 (1970).
(1085) S. Walker, *J. Pharm. Pharmacol.*, **22,** 574(1970).
(1086) I. Sugimoto, *Chem. Pharm. Bull.*, **18,** 515(1970).
(1087) K. Kakemi, H. Sezaki, M. Nakano, and E. Suzuki, *ibid.*, **18,** 2176(1970).
(1088) D. Winne and J. Remischovsky, *J. Pharm. Pharmacol.*, **22,** 640(1970).
(1089) W. Crouthamel, J. Doluisio, R. Johnson, and L. Diamond, *J. Pharm. Sci.*, **59,** 878(1970).
(1090) S. Chung, Y. Park, and S. Hong, *Amer. J. Physiol.*, **219,** 30(1970).
(1091) A. Beckett, J. Taylor, and P. Kourounakis, *J. Pharm. Pharmacol.*, **22,** 123(1970).
(1092) A. Axelrad, A. Lawrence, and R. Hazelwood, *Amer. J. Physiol.*, **219,** 860(1970).
(1093) W. Jusko, J. Leonards, and G. Levy, *J. Pharm. Sci.*, **59,** 566(1970).
(1094) W. Jusko, G. Levy, and S. Yaffe, *ibid.*, **59,** 487(1970).
(1095) A. Thomson, H. Baker, and C. Leevy, *J. Lab. Clin. Med.*, **76,** 34(1970).
(1096) I. Stockley, *Amer. J. Hosp. Pharm.*, **27,** 977(1970).
(1097) L. Garrettson and P. Dayton, *Clin. Pharmacol. Ther.*, **11,** 674(1970).
(1098) F. Boioli, B. Damascelli, P. Pozzoli, and L. Roncoroni, *Med. Nucl., Radiobiol. Lat.*, **10,** 207(1967); through *Chem. Abstr.*, **73,** 54548k(1970).
(1099) E. Illes, *Acta Vet.*, **20,** 139(1970); through *Chem. Abstr.*, **73,** 107902e(1970).
(1100) W. Hayton, D. Guttman, and G. Levy, *J. Pharm. Sci.*, **59,** 575(1970).
(1101) A. Perala, *Farm. Aikak.*, **78,** 278(1969); through *Chem. Abstr.*, **72,** 130656r(1970).
(1102) D. Read, M. Hays, and J. Hershman, *J. Clin. Endocrinol.*, **30,** 798(1970).
(1103) A. Ruiz-Torres and J. Ohlmeier, *Arzneim.-Forsch.*, **20,** 522(1970); through *Chem. Abstr.*, **73,** 12736q(1970).
(1104) F. Yamasaku, *Nippon Kagaku Ryohogakukai Zasshi*, **18,** 302(1970); through *Chem. Abstr.*, **73,** 86444q(1970).
(1105) S. Srikantia and V. Reddy, *Amer. J. Clin. Nutr.*, **23,** 114(1970); through *Chem. Abstr.*, **72,** 77319e(1970).
(1106) L. Borella, J. Pinski, and F. Herr, *Res. Commun. Chem. Pathol. Pharmacol.*, **1,** 667(1970); through *Chem. Abstr.*, **73,** 118749m(1970).
(1107) A. Allenby, N. Creasey, J. Edginton, J. Fletcher, and C. Schock, *Brit. J. Dermatol., Suppl.*, **47,** 81(1969); through *Chem. Abstr.*, **72,** 119712k(1970).
(1108) I. Yamagami, Y. Suzuki, M. Ito, and H. Fujimura, *Nippon Yakurigaku Zasshi*, **65,** 236(1960); through *Chem. Abstr.*, **73,** 43738w(1970).
(1109) P. Febvre, J. Aiache, and P. Jabor, *Labo-Pharma-Probl. Tech.*, **18,** 69(1970); through *Chem. Abstr.*, **73,** 75434k(1970).
(1110) E. Ariens, *J. Mond. Pharm.*, **12,** 263(1969); through *Chem. Abstr.*, **72,** 119635n(1970).
(1111) J. Ashford, M. Hossain, J. Roberts, B. Thomas, and A. Wilson, *Biochem. Pharmacol.*, **19,** 2069(1970); through *Chem. Abstr.*, **73,** 75315x(1970).
(1112) A. Colombi, R. Tagliavinia, and P. Lucchelli, *Boll. Chim Farm.*, **108,** 632(1969); through *Chem. Abstr.*, **73,** 7182b(1970).
(1113) A. Conney, *J. Mond. Pharm.*, **12,** 186(1969); through *Chem. Abstr.*, **72,** 119988e(1970).
(1114) L. Diamond, J. Doluisio, and W. Crouthamel, *Eur. J. Pharmacol.*, **11,** 109(1970); through *Chem. Abstr.*, **73,** 75586m(1970).
(1115) W. Eickenbusch, H. Lahrtz, U. Seppelt, and P. Van Zwieten, *Klin. Wochenschr.*, **48,** 270(1970); through *Chem. Abstr.*, **72,** 119687f(1970).
(1116) L. Gangarosa and D. Cheong, *Proc. Soc. Exp. Biol. Med.*, **133,** 1169(1970); through *Chem. Abstr.*, **73,** 43750u(1970).
(1117) T. Gloria, *Rev. Brasil. Farm.*, **50,** 351(1969); through *Chem. Abstr.*, **73,** 28805x(1970).
(1118) F. Gross, *J. Mond. Pharm.*, **12,** 229(1969); through *Chem. Abstr.*, **72,** 119634m(1970).
(1119) A. Havel and M. Rosenfeld, *Arzneim.-Forsch.*, **20,** 1167 (1970); through *Chem. Abstr.*, **73,** 129290f(1970).
(1120) S. Hollobaugh, M. Rao, and F. Kruger, *Diabetes*, **19,** 45(1970); through *Chem. Abstr.*, **72,** 53640b(1970).
(1121) C. Klaassen, *J. Pharmacol. Exp. Ther.*, **175,** 289(1970); through *Chem. Abstr.*, **73,** 129205g(1970).
(1122) F. Koss, D. Maver, H. Haindl, and T. Kabbara, *Arzneim.-Forsch.*, **20,** 1218(1970); through *Chem. Abstr.*, **73,** 129197f(1970).
(1123) P. Lamy and D. Blake, *J. Amer. Pharm. Ass.*, **NS10,** 72(1970).
(1124) G. Keusch, F. Troncale, and R. Buchanan, *Arch. Intern. Med.*, **125,** 273(1970); through *Chem. Abstr.*, **72,** 88795h(1970).
(1125) S. McLean and C. Marchand, *Life Sci.*, **9,** 1075(1970); through *Chem. Abstr.*, **73,** 119004b(1970).
(1126) A. Mudd and R. Gibbons, *Res. Vet. Sci.*, **10,** 576(1969); through *Chem. Abstr.*, **72,** 77294t(1970).
(1127) A. Phansalkar and J. Balwani, *Hindustan Antibiot. Bull.*, **12,** 179(1970); through *Chem. Abstr.*, **73,** 118977j(1970).
(1128) M. Peters and J. Fouts, *Biochem. Pharmacol.*, **19,** 533 (1970); through *Chem. Abstr.*, **72,** 119710h(1970).
(1129) I. Phillips, M. Ridley, D. Rimmer, R. Lynn, and C. Warren, *Lancet*, **1,** 263(1970).
(1130) H. Takizawa, M. Niwayama, O. Kitami, A. Takano, and H. Ochiai, *Niigata Igakkai Zasshi*, **84,** 52(1970); through *Chem. Abstr.*, **73,** 2292c(1970).
(1131) R. Schnell and T. Miya, *Biochem. Pharmacol.*, **19,** 303 (1970).
(1132) R. Schnell and T. Miya, *J. Pharmacol. Exp. Ther.*, **174,** 177(1970); through *Chem. Abstr.*, **73,** 75193f(1970).
(1133) E. Schulz and F. Schmidt, *Pharmacol. Clin.*, **2,** 150(1970); through *Chem. Abstr.*, **73,** 75572d(1970).
(1134) F. Valdes and F. Orrego, *Nature (London)*, **226,** 761(1970); through *Chem. Abstr.*, **73,** 23691x(1970).
(1135) M. Soscia, R. Rava, E. Rogliani, and F. Giordano, *Biochem. Appl.*, **15,** 197(1968); through *Chem. Abstr.*, **73,** 75319b (1970).
(1136) S. Waxman, J. Corcino, and V. Herbert, *Amer. J. Med.*, **48,** 599(1970); through *Chem. Abstr.*, **73,** 54123t(1970).
(1137) E. Wolff-Soerensen, *Nord. Med.*, **83,** 171(1970); through *Chem. Abstr.*, **73,** 2578a(1970).
(1138) G. Will and K. Boddy, *Amer. J. Clin. Nutr.*, **23,** 779(1970); through *Chem. Abstr.*, **73,** 13060b(1970).
(1139) J. Sjogren, *Farm. Revy*, **69,** 480(1970); through *Chem. Abstr.*, **73,** 129166v(1970).
(1140) K. Schemmel, E. Haupt, and K. Leybold, *Klin. Wochenschr.*, **48,** 434(1970); through *Chem. Abstr.*, **73,** 33633u(1970).
(1141) J. Salser and M. Balis, *Biochem. Pharmacol.*, **19,** 2375 (1970); through *Chem. Abstr.*, **73,** 86082v(1970).
(1142) D. Hussar, *J. Amer. Pharm. Ass.*, **NS10,** 78(1970).
(1143) W. Ritsche, *Angew. Chem., Int. Ed. Engl.*, **8,** 699(1969); through *Chem. Abstr.*, **72,** 6201z(1970).
(1144) F. Laurencet and J. Fabre, *J. Urol. Nephrol.*, **74,** 1038 (1968); through *Chem. Abstr.*, **72,** 119686e(1970).
(1145) M. Lader, G. Sakalis, and M. Tansella, *Psychopharmacologia*, **18,** 118(1970); through *Chem. Abstr.*, **73,** 86052k(1970).
(1146) W. Barr and S. Riegelman, *J. Pharm. Sci.*, **59,** 164(1970).
(1147) K. Kakemi, H. Sezaki, R. Konishi, T. Kimura, and M. Murakami, *Chem. Pharm. Bull.*, **18,** 275(1970).
(1148) R. O'Reilly and G. Levy, *J. Pharm. Sci.*, **59,** 1258(1970).
(1149) K. Kakemi, H. Sezaki, S. Muranishi, and A. Yano, *Chem. Pharm. Bull.*, **18,** 1563(1970).

(1150) J. Thierry, M. Hermodson, and J. Suttie, *Amer. J. Physiol.*, **219,** 854(1970).
(1151) R. Levine and C. Dizon, *J. Pharm. Sci.*, **59,** 1845(1970).
(1152) K. Kakemi, H. Sezaki, R. Konishi, T. Kimura, and A. Okita, *Chem. Pharm. Bull.*, **18,** 1034(1970).
(1153) M. Kauker, W. Lassiter, and C. Gottschalk, *Amer. J. Physiol.*, **219,** 45(1970).
(1154) E. Menczel and H. Maibach, *J. Invest. Dermatol.*, **51,** 386(1970).
(1155) T. Arita, R. Hori, K. Ito, and H. Sekikawa, *Chem. Pharm. Bull.*, **18,** 1675(1970).
(1156) K. Ikeda, K. Miyata, T. Iwata, F. Kawata, and K. Kurome, *ibid.*, **18,** 440(1970).
(1157) F. Kruger, R. Altschuld, S. Hollobaugh, and B. Jewett, *Diabetes*, **19,** 50(1970); through *Chem. Abstr.*, **72,** 53641c(1970).
(1158) G. Mannering, *Present Status Psychotropic Drugs, Proc. Int. Congr., Coll. Int. Neuro-Psychopharmacol., 6th,* **1968,** 107; through *Chem. Abstr.*, **73,** 118703s(1970).
(1159) W. Jubiz, R. Levinson, A. Meikle, C. West, and F. Tyler, *Endocrinology*, **86,** 328(1970); through *Chem. Abstr.*, **72,** 88680s (1970).
(1160) K. Isselbacher, *Progr. Biochem. Pharmacol.*, **3,** 177(1967); through *Chem. Abstr.*, **72,** 119912a(1970).
(1161) L. Davis and W. Wolff, *Amer. J. Vet. Res.*, **31,** 469(1970); through *Chem. Abstr.*, **72,** 130649r(1970).
(1162) C. Coutinho, J. Cheripko, and J. Carbone, *Biochem. Pharmacol.*, **19,** 363(1970); through *Chem. Abstr.*, **72,** 130691y(1970).
(1163) E. Garrett, *Develop. Saf. More Eff. Drugs, Symp.*, **1967,** 99; through *Chem. Abstr.*, **72,** 1823u(1970).
(1164) J. Caldwell, T. Halpin, and N. Greenberger, *J. Lab. Clin. Med.*, **75,** 43(1970).
(1165) W. Barr and S. Riegelman, *J. Pharm. Sci.*, **59,** 154(1970).
(1166) R. Willix, *ibid.*, **59,** 1439(1970).
(1167) M. Taraszka, *ibid.*, **59,** 873(1970).
(1168) C. Morris, J. Christian, T. Miya, and W. Hansen, *ibid.*, **59,** 325(1970).
(1169) Y. Martin and R. Wiegand, *ibid.*, **59,** 1313(1970).
(1170) H. Downer, R. Galloway, L. Horwich, and D. Parke, *J. Pharm. Pharmacol.*, **22,** 479(1970).
(1171) H. Shindo, T. Komai, E. Nakajima, H. Murata, A. Yasumura, and I. Seki, *Yakugaku Zasshi*, **90,** 36(1970).
(1172) N. Marceau, N. Aspin, and A. Sass-Kortsak, *Amer. J. Physiol.*, **218,** 377(1970).
(1173) T. Arita, R. Hori, T. Anmo, M. Washitake, M. Akatsu, and T. Yajima, *Chem. Pharm. Bull.*, **18,** 1045(1970).
(1174) J. Coliazzi, *J. Pharm. Ed.*, **34,** 185(1970).
(1175) W. Forth, E. Furukawa, W. Rummel, and H. Andres, *Naunyn-Schmiedebergs Arch. Pharmakol.*, **264,** 406(1969); through *Chem. Abstr.*, **72,** 1858j(1970).
(1176) E. Eperjessy, Z. Dakay, and B. Honti, *Acta Pharm. Hung.*, **40,** 12(1970); through *Chem. Abstr.*, **73,** 69802n(1970).
(1177) J. Baldridge, *Bull. Parenteral Drug Ass.*, **23,** 40(1969); through *Chem. Abstr.*, **73,** 86042g(1970).
(1178) N. Billups and N. Patel, *J. Pharm. Ed.*, **34,** 190(1970).
(1179) R. Boyes, H. Adams, and B. Duce, *J. Pharmacol. Exp. Ther.*, **174,** 1(1970); through *Chem. Abstr.*, **73,** 64552w(1970).
(1180) A. Knight, C. Vickers, and A. Percival, *Brit. J. Dermatol., Suppl.*, **81,** 88(1969); through *Chem. Abstr.*, **72,** 103668q(1970).
(1181) R. Levine, *Amer. J. Dig. Dis.*, **15,** 171(1970); through *Chem. Abstr.*, **72,** 119623g(1970).
(1182) M. Mayersohn and M. Gibaldi, *Biochim. Biophys. Acta*, **196,** 296(1970); through *Chem. Abstr.*, **72,** 109326y(1970).
(1183) C. Moriwaki and K. Yamaguchi, *Horumon To Rinsho*, **18,** 205(1970); through *Chem. Abstr.*, **73,** 54415q(1970).
(1184) E. Novak, J. Wagner, and D. Lamb, *Int. Z. Klin. Pharmakol. Ther. Toxikol.*, **3,** 201(1970); through *Chem. Abstr.*, **73,** 129480t (1970).
(1185) S. Rasmussen, *Ugeskr. Laeger*, **131,** 1994(1969); through *Chem. Abstr.*, **72,** 93298c(1970).
(1186) M. Schou, *Present Status Psychotropic Drugs, Proc. Int. Congr. Coll. Int. Neuro-Psychopharmacol., 6th,* **1968,** 120; through *Chem. Abstr.*, **73,** 118745g(1970).
(1187) P. Van Caneghem, *Louvain Med.*, **88,** 763(1969); through *Chem. Abstr.*, **73,** 2570s(1970).
(1188) O. Stalheim, *Amer. J. Vet. Res.*, **31,** 497(1970); through *Chem. Abstr.*, **72,** 130777f(1970).
(1189) T. Slotkin, V. Di-Stefano, and W. Au, *J. Pharmacol. Exp. Ther.*, **173,** 26(1970); through *Chem. Abstr.*, **73,** 43815u(1970).
(1190) H. Stricker, *Arzneim.-Forsch.*, **20,** 391(1970); through *Chem. Abstr.*, **73,** 18471w(1970).
(1191) E. Usdin, *Psychopharmacol. Bull.*, **6,** 4(1970); through *Chem. Abstr.*, **73,** 86033e(1970).
(1192) G. Damia, G. Torri, G. Frova, and R. Palleni, *Minerva Anestesiol.*, **36,** 1(1970); through *Chem. Abstr.*, **73,** 33558y(1970).
(1193) A. Haerer, R. Buchanan, and F. Wiygul, *J. Clin. Pharmacol. J. New Drugs*, **10,** 370(1970).
(1194) E. Randinitis, M. Barr, H. Wormser, and J. Nagwekar, *J. Pharm. Sci.*, **59,** 806(1970).
(1195) E. Randinitis, M. Barr, and J. Nagwekar, *ibid.*, **59,** 813 (1970).
(1196) J. Nagwekar and H. Kostenbauder, *ibid.*, **59,** 1775(1970).
(1197) W. Jusko and G. Levy, *ibid.*, **59,** 765(1970).
(1198) E. Garrett, S. Heman-Ackah, and G. Perry, *ibid.*, **59,** 1448(1970).
(1199) A. Beckett and A. Moffat, *J. Pharm. Pharmacol.*, **22,** 15(1970).
(1200) J. Doluisio, W. Crouthamel, G. Tan, J. Swintosky, and L. Dittert, *J. Pharm. Sci.*, **59,** 72(1970).
(1201) B. Ballard and E. Menczel, *ibid.*, **59,** 714(1970).
(1202) R. Turner, C. Mehta, and L. Benet, *ibid.*, **59,** 590(1970).
(1203) A. Goossens and M. van Oudtshoorn, *J. Pharm. Pharmacol.*, **22,** 224(1970).
(1204) S. Kaplan, R. Weinfeld, S. Cotler, C. Abruzzo, and K. Alexander, *J. Pharm. Sci.*, **59,** 358(1970).
(1205) S. Naito, M. Mizutani, S. Osumi, K. Umetsu, T. Mikawa, Y. Nishimura, and N. Yamamoto, *ibid.*, **59,** 1742(1970).
(1206) H. Nogami, M. Hanano, S. Awazu, and T. Iga, *Chem. Pharm. Bull.*, **18,** 228(1970).
(1207) W. Kuebler, *Z. Kinderheilk.*, **108,** 187(1970); through *Chem. Abstr.*, **73,** 97026f(1970).
(1208) M. Mayersohn and M. Gibaldi, *J. Pharm. Ed.*, **34,** 608 (1970).
(1209) R. O'Reilly and G. Levy, *Clin. Pharmacol. Ther.*, **11,** 378(1970).
(1210) C. von Bahr, F. Sjoqvist, and G. Levy, *J. Pharm. Pharmacol.*, **22,** 867(1970).
(1211) W. Ritschel, *Drug Intel. Clin. Pharm.*, **4,** 332(1970).
(1212) K. Arnold and N. Gerber, *Clin. Pharmacol. Ther.*, **11,** 121(1970).
(1213) A. Beckett, P. Kourounakis, D. Vaughan, and M. Mitchard, *J. Pharm. Pharmacol.*, **22,** 169s(1970).
(1214) D. Gilboe and A. Betz, *Amer. J. Physiol.*, **219,** 774(1970).
(1215) M. Bartek, L. Miller, and P. Weiss, *Toxicol. Appl. Pharmacol.*, **17,** 41(1970).
(1216) A. Beckett, *Present Status Psychotropic Drugs, Proc. Int. Congr. Coll. Int. Neuro-Psychopharmacol., 6th,* **1968,** 53; through *Chem. Abstr.*, **72,** 64945f(1970).
(1217) A. Beckett, *Pure Appl. Chem.*, **19,** 231(1969); through *Chem. Abstr.*, **72,** 119656v(1970).
(1218) J. Buell and R. Kalaba, *Math. Biosci.*, **5,** 121(1969); through *Chem. Abstr.*, **72,** 64973p(1970).
(1219) H. Jun, J. Hlynka, and E. Triggs, *Can. J. Pharm. Sci.*, **4,** 27(1969); through *Chem. Abstr.*, **72,** 11298r(1970).
(1220) W. Klinger, *Arch. Int. Pharmacodyn. Ther.*, **180,** 309 (1969); through *Chem. Abstr.*, **72,** 20214n(1970).
(1221) G. Levy, *J. Pharm. Sci.*, **59,** 1847(1970).
(1222) P. Lewi, J. Heykants, F. Allewijn, J. Dony, and P. Janssen, *Arzneim.-Forsch.*, **20,** 943(1970); through *Chem. Abstr.*, **73,** 75304t (1970).
(1223) T. Modzelewski and Z. Wojtowicz, *Acta Med. Pol.*, **11,** 29(1970); through *Chem. Abstr.*, **73,** 75184d(1970).
(1224) G. Moessner, V. Buerkey, K. Egetmeyer, and H. Maurer, *Arzneim.-Forsch.*, **19,** 1949(1969); through *Chem. Abstr.*, **72,** 53629e(1970).
(1225) C. Museteanu and N. Bonciocat, *Farmacia (Bucharest)*, **18,** 129(1970); through *Chem. Abstr.*, **73,** 43468h(1970).
(1226) O. Kitamoto and K. Fukaya, *Nippon Kagaku Ryohogakukai Zasshi*, **18,** 145(1970); through *Chem. Abstr.*, **73,** 43729u(1970).
(1227) J. Paterson, M. Conolly, C. Dollery, A. Hayes, and R. Cooper, *Pharmacol. Clin.*, **2,** 127(1970); through *Chem. Abstr.*, **73,** 75571c(1970).
(1228) D. Schwartz and W. Ziegler, *Postgrad. Med. J., Suppl.*, **45,** 32(1969); through *Chem. Abstr.*, **72,** 130999e(1970).

(1229) J. Tuomisto, *Duodecim*, **86**, 179(1970); through *Chem. Abstr.*, **73**, 43417r(1970).
(1230) E. Van der Kleijn, *Arch. Int. Pharmacodyn. Ther.*, **178**, 457(1969); through *Chem. Abstr.*, **72**, 41377h(1970).
(1231) K. Vollmer and A. Poisson, *Arzneim.-Forsch.*, **20**, 992 (1970); through *Chem. Abstr.*, **73**, 86422f(1970).
(1232) T. Suzuki, Y. Saitoh, and K. Nishihara, *Chem. Pharm. Bull.*, **18**, 405(1970); through *Chem. Abstr.*, **72**, 130974t(1970).
(1233) L. Mombelli, M. Fidanza, G. Rencari, and G. Bagliani, *Med. Nucl., Radiobiol. Lat.*, **11**, 153(1968); through *Chem. Abstr.*, **72**, 29978x(1970).
(1234) B. Cabana and P. Gessner, *J. Pharmacol. Exp. Ther.*, **174**, 260(1970); through *Chem. Abstr.*, **73**, 75408e(1970).
(1235) K. Balasubramaniam, S. Lucas, G. Mawer, and P. Simons, *Brit. J. Pharmacol.*, **39**, 564(1970); through *Chem. Abstr.*, **73**, 75188h(1970).
(1236) J. Estes, *J. Amer. Med. Ass.*, **212**, 1492(1970); through *Chem. Abstr.*, **73**, 33836n(1970).

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Editor's Note: The scope of this article has been limited to a review of the literature in the area of pharmaceutics because reviews of the literature related to other areas of the pharmaceutical sciences are published elsewhere annually.

RESEARCH ARTICLES

Kinetics of Absorption and Excretion of Levodopa in Dogs

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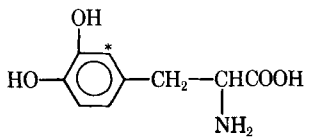
Abstract □ The rate and extent of levodopa absorption and excretion following intravenous and oral administration of 2-^{14}C-levodopa to acute and chronically treated dogs were investigated. Plasma levels of intact levodopa following the intravenous administration declined rapidly during the first 4–6 hr. The elimination-rate constant of intact levodopa from the plasma ranged between 0.73 and 0.99 hr.$^{-1}$, which corresponds to a half-life of approximately 40–60 min. The elimination-rate constant of total plasma ^{14}C ranged between 0.007 and 0.085 hr.$^{-1}$, which corresponds to a half-life of 8–9 hr., indicating that the total ^{14}C was eliminated at one-tenth the rate of intact levodopa. Peak plasma levels of intact levodopa and of total plasma ^{14}C following oral administration were attained 25–30 min. after dosing. Approximately 70–75% of the intravenous and 57–70% of the oral radioactive doses were excreted in urine over a 72-hr. period. Levodopa and dopamine accounted for a very small percentage of the radioactivity in the urine. Approximately 3.0–7.0% of the intravenous or oral radioactive dose was excreted in the feces. The efficiency of absorption of total radioactivity was calculated to range between 83.0 and 92.0%. Analysis of the ratio of intact levodopa levels to total ^{14}C levels indicated that only 22.0–30.0% of the administered dose reached the general circulation as intact levodopa, suggesting that the remainder of the absorbed dose, approximately 60.0%, is biotransformed in the gastrointestinal tract prior to absorption and/or in the liver during its "first passage" to the general circulation.

Keyphrases □ Levodopa, absorption and excretion, dogs—pharmacokinetics □ Pharmacokinetics—labeled levodopa absorption and excretion, dogs □ Absorption kinetics, labeled levodopa—oral, intravenous administration □ Excretion kinetics, labeled levodopa—oral, intravenous administration

Discovery of the presence of dopamine in the striatum and substantia nigral areas of the brain (1, 2) and of its depletion in patients with Parkinson's disease (3, 4) and in experimental animals following nigral lesions (5) provided new therapeutic approaches to Parkinsonism. Among the several means considered for correcting dopamine areas was the administration of the immediate precursor of dopamine, levodopa[1].

Consideration of the need for large doses of levodopa to attain therapeutic efficacy when given orally led to this investigation of the absorption and excretion of levodopa. The study was conducted under two experimental conditions: after the administration of a single dose and following chronic treatment of animals with levodopa. It was expected that the data obtained following the intravenous and oral administration of 2-^{14}C-levodopa (I) to dogs would yield the following information: (*a*) total plasma ^{14}C and intact levodopa levels and corresponding half-lives of elimination, (*b*) rate and extent of absorption from the gastrointestinal tract following oral administration of drug, (*c*) percent recovery of drug in urine, and (*d*) rate and extent of levodopa metabolism.



2-^{14}C-levodopa (*denotes position of radioactive label)
I

MATERIALS AND METHODS

Acute Single-Dose Study—Two beagle dogs, weighing 8–10 kg., were each given a single intravenous and oral 50-mg./kg. dose of 2-^{14}C-levodopa (Lot B-1, specific activity 0.19 μc./mg.). The dose (50 mg./kg.) selected was within the average range of the therapeutic dose administered to humans with Parkinson's disease, and it was

[1] L-3,4-Dihydroxyphenylalanine.