Journal of Pharmaceutical Sciences

AUGUST 1973
VOLUME 62 NUMBER 8

REVIEW ARTICLE

Pharmaceutical Sciences—1972: Literature Review of Pharmaceutics II‡

ASHOK C. SHAH*▲ and ALLEN K. HERD†

Keyphrases ☐ Pharmaceutical sciences—1972 literature review of pharmaceutics ☐ Technology, pharmaceutical—sterility, dosage forms, packaging equipment ☐ Physical pharmacy—dissolution, solubility, permeability, complexation, surface phenomena ☐ Antibiotics—pharmaceutical aspects ☐ Radiopharmaceuticals—pharmaceutical aspects ☐ Biopharmaceutics—drug properties, absorption, pharmacokinetics ☐ Literature review—pharmaceutical sciences 1972

CONTENTS

‡ *Editor's note:* Part I of this article appeared in the July 1973 issue of the *Journal of Pharmaceutical Sciences*.

PHYSICAL PHARMACY (*continued*)

Membrane Permeation—Phenomena associated with membrane permeability are important pharmaceutically in drug transport modeling and in the design of effective drug delivery systems. Flynn and his coworkers studied the influence of solvent composition and permeant solubility on membrane transport (850) and the influence of alkyl chain length on flux-determining properties of the barrier and diffusant (851), and they derived equations describing the diffusion layer control flux of a permeant through a membrane sandwiched between two liquid phases (852). It was shown that, under certain conditions, the steady-state transfusion through dimethylpolysiloxane membranes by *p*-aminoacetophenone from binary solvent mixtures was essentially controlled by the thermodynamic activity of the compound in the applied phase (850). A theoretical expression was presented correlating the effect of alkyl chain length on partition coefficient, solubility, and maximum steady-state flux through a model membrane. This expression, predicting a parabolic dependency of the flux with respect to alkyl chain length, was experimentally verified by determining transport rates of an homologous series of esters across the dimethylpolysiloxane membrane (851). Equations derived for the diffusion layer control flux of a permeant through a membrane sandwiched between two liquid phases confirmed that the steady-state flux in such cases is only dependent on the applied phase concentration, the diffusivity within the diffusion layers, and the reciprocal of the sum of the diffusion layer thicknesses. Furthermore, a lag time expression was derived which relates the duration of the nonsteady state to the membrane and diffusion layer

thicknesses, the membrane–solvent partition coefficient, and the reciprocal of diffusivity within the solvent. The significance of the lag time effect as the limiting factor in the structure–activity profile for a series of organic homologs was discussed (852).

The changes in *in vitro* permeability rates of benzocaine through silicone rubber implants by introduction of copermeant plasticizers into the implant were investigated. Solubility, diffusivity, molecular volumes and mobilities of the copermeants, hydrogen-bonding capabilities, and potential for internal segmental motion of polymeric plasticizers were considered as the factors influencing drug transmission rates (853). Studies on permeation of aniline and substituted anilines (854), aromatic acids, alcohols, amines, esters, aldehydes, and ketones (855) were performed to ascertain the effect of chemical structure on the permeation of these agents through polyethylene. The permeability constants of these compounds were shown to correlate with their hexane–water partition coefficients by an empirical equation (855). A thermogravimetric analysis method was used to evaluate the diffusion and solubility of a series of aliphatic alcohols in a specific polyurethane film at several different temperatures. In general, the diffusion coefficients of the straight-chain alcohols increased with temperature and decreased with molecular weight. By knowing solubility and diffusion coefficients, the permeability constants were estimated (856).

The effects of changes in the polymer ratio and environmental conditions on the water vapor transmission properties of plasticized films containing combinations of hydroxypropyl methylcellulose and ethylcellulose were evaluated. The findings of this study demonstrated the presence of another mechanism of vapor transmission, in addition to diffusion, which is apparently related to the hydrophilic character of the film (857). Water vapor transmission through cellulose acetate phthalate and *n*-butyl methacrylate polymer films showed significant differences in permeability behavior with the cellulose acetate phthalate films, depending on whether moisture was present on one or both sides of the film during permeation; however, this effect did not occur with the *n*-butyl methacrylate films. The dehydration of the distal cellulose acetate phthalate film surface when moisture is present only on the proximal surface was provided as an explanation for the permeability behavior of the membrane (858). A method was described for the study of free unsupported polymer films; its applicability was demonstrated by testing effects of spray rate and film substrate on mechanical strength and water permeability of cellulose acetate films (859).

The hindrance of solute diffusion was measured through microporous membranes of known pore geometry with pore radii ranging from 2.5 to 300 Å. The membranes were prepared by bombardment of mica sheets with fission fragments from a ^{235}U source and subsequent etching with hydrofluoric acid. It was concluded that in most membrane operations there is a considerable resistance to diffusion due to the presence of a liquid film boundary layer along the surface of the membrane. However, this boundary layer resistance was not inversely proportional to the solute diffusivity, as has been often assumed in the unstirred layer theory,

Table XXV—Additional References on Membrane Permeability

Reference	Topic
868	Review emphasizing physicochemical properties of drugs and cell membranes that control or modify transmembrane movement
869	Review of theories and characteristics of monolayer permeation of water, gases, and ions
870	Review of theoretical considerations and experimental studies of vapor and gas permeability of commonly used plastics
871	Review of the permeability of polymeric packaging materials to gases and organic vapors
872	Review emphasizing aspects of selective permeability of biological and synthetic membranes
873	Ion transport across biological membranes
874	Evaluation of water vapor transmission, hardness, drug release rates, and other physical properties of polymeric films in the formulation of an aerosol occlusive dressing
875	Influence of hydrophobic interactions on the electrochemical selectivity ratios of liquid membranes responsive to organic ions
876	Sodium- and chloride-ion permeabilities measured across both charged and uncharged unmodified phospholipid bilayers
877	Diffusion of small nonelectrolytes across liposome membranes indicating structure of such biological membranes similar to smectic mesophases and hydrophobic polymer networks
878	Permeability of alkali metal and ammonium salt electrolytes through polyphthalamide microcapsule membranes suggesting formation of a stable diffusion layer of electrolytes in the interior of the microcapsules

but was proportional to the −0.6 power of the solute diffusivity (860). A new theory based on absolute reaction rates was proposed to explain diffusion of polystyrene spheres through a thin membrane with cylindrical pores (861). Two different models for the diffusion of a binary solution through a membrane were used to derive relations between the solute permeability coefficient and the reflection coefficient. The theoretical considerations were shown to agree with previously reported data for highly porous membranes (862).

The transport rates of sodium and potassium chlorides through the bovine eye-lens capsule, insoluble gelatin membrane, and collagen membrane were measured to estimate the permeability coefficient, the rate constant of permeation at the interface, the apparent membrane constant, and the interface constant. The permeability of the bovine eye-lens capsule was greater than the gelatin membrane but was comparable to the collagen membrane (863). In a subsequent study, ionic diffusion and permeability of potassium hydrogen aspartate and magnesium hydrogen aspartate across the vitreous bovine eye-lens capsule was investigated (864). The permeability of potassium chloride through two-component membranes, composed of gelatin and chondroitin sulfate C, was measured. The membrane permeability was decreased with an increase of total weight of the membrane and with an increase of the amount of chondroitin sulfate C (865).

The effect of salicylate on the relative cation permeability of a membrane was investigated in large, identified molluscan neurons. Salicylate caused a reversible, dose-dependent decrease in the permeability of rubidium, cesium, sodium, and lithium ions relative to

that of potassium ions, probably due to the adsorption of salicylate anions to the membrane with a subsequent increase in the density and field strength of anionic sites in the membrane (866). Salicylate, benzoate, and their analogs reversibly increased the membrane potential and conductance of identified molluscan neurons by increasing potassium conductance and decreasing chloride conductance. The relative potencies of these compound's were closely correlated with their octanol–water partition coefficients and their pKa values (867).

Additional membrane permeability studies are listed in Table XXV.

Complexation—The studies related to complexation phenomena are categorized into: (*a*) interactions of drugs with biological substances, and (*b*) interactions of drugs with nonbiological substances.

Interactions of Drugs with Biological Substances—Computer programs were used to compute and plot theoretical data in which the binding capacities, association constants, and level of protein were varied in a system of dicumarol (bishydroxycoumarin) and human serum albumin. In general, for any one drug level the amount of unbound drug was inversely proportional to the binding capacity, association constant, and protein content (879). The *in vitro* binding of a number of sulfa drugs to human serum albumin was studied as a function of pH, and the results were correlated with pKa, octanol–water partition coefficient, and electron distribution of the sulfa drug. It was concluded that the primary effect in sulfa drug binding with human serum albumin may be an electrostatic attraction between the anionic drug molecule and a cationic site of human serum albumin, while hydrogen bonding and attraction between the tryptophan residue of human serum albumin and the sulfa drug play a secondary role (880–882).

Interaction between 5-dimethylamino-1-naphthalenesulfonamide and human serum albumin suggested that the binding of the drug to the protein is hydrophobic in nature, and it occurs near the tryptophan residue of the protein (883). The binding constants of various sulfonamide drugs with bovine serum albumin determined as a function of pH were analyzed with five energy-related physicochemical parameters, taking into account the correction for ionization of the drugs. It was postulated that the binding equilibrium depends on the hydrophobicity of the drug and binding occurs between the neutral drug molecule and the hydrophobic fraction of the protein surface (884). The binding of 33 organic compounds to bovine serum albumin was studied at pH 7.4 and 37°. The binding affinity of these compounds correlated with their octanol–water partition coefficients when more than 50% of the compound existed as unionized molecules at pH 7.4. It was shown that the octanol–water and isobutanol–water reference systems for defining hydrophobic character yield comparable results (885).

The interaction of tritiated prostaglandin E_1 with various constituents of human blood was examined by equilibrium dialysis and incubation experiments. Prostaglandin E_1 apparently exhibited weak interactions with serum albumin but did not interact with blood cells and plasma globulins (886). Following incubation of tritiated digoxin with human blood, all the radioactivity was found associated with the plasma, with 25% bound to the serum albumin and the rest free in solution. Addition of cortisol, progesterone, or cholesterol to the serum decreased digoxin binding (887). However, analysis of the serum obtained from human subjects 2 hr. after receiving tritiated digoxin orally or by intravenous injection showed only 1–10% of the drug bound to serum protein (888). The plasma protein binding of diphenylhydantoin in adult patients with epilepsy, in normal subjects, and in hyperbilirubinemic newborn infants was investigated. Competition was indicated between the drug and bilirubin for albumin binding sites (889). The binding of estrone sulfate by human serum albumin appeared to involve one strong binding site and several weaker binding sites. Estradiol 3-sulfate, androsterone sulfate, and similar other compounds were shown to compete for estrone sulfate binding (890).

The binding of salicylic acid to human serum albumin was studied by equilibrium dialysis and frontal gel chromatography. The reproducibility of the data provided by chromatography was far superior to that obtained with equilibrium dialysis (891). An ultrafiltration method, using membranes that quantitatively separate small molecules from plasma proteins, was employed to measure plasma binding of salicylate. The results obtained by this method were comparable to those obtained by equilibrium dialysis (892). The proportion of salicylate bound to serum proteins of rats *in vitro* increased with the increasing age of the rats, from 30% at 7 days to 53.2% at 60 days, due to increased serum albumin concentrations in the older rats. These results may partially explain the greater drug sensitivity of newborn animals (893). Three sulfonylureas, acetohexamide, chlorpropamide, and tolbutamide, were investigated in terms of their affinity for the major human serum proteins. At pH 6.5, 7.4, and 8.4 and normal human serum protein concentrations, these drugs were primarily bound to albumin. Inhibition of sulfonylurea–albumin binding by drugs that are known to potentiate activity of these sulfonylureas was studied (894). The serum albumin binding capacity of doxycycline, metoclopramide, sulfaethylthiazole, and progesterone was increased approximately 40% in the presence of physiological concentrations of urea. Disorganization of the protein structures by a reduction of intramolecular hydrophobic forces was suggested as a probable reason for the urea-induced increase of the drug–protein binding (895). Antileprous drugs and thyroxine bind to human serum proteins at a common site. This was demonstrated by mutual interference between thyroid hormones and antileprous drugs in binding to human serum (896). On the basis of affinity for serum proteins, antileprous drugs were classified into: the albumin-affinitive type, the globulin-affinitive type, the nonadsorbing type, and those having moderate affinity to serum proteins (897).

In lecithin–water model membrane systems, polymyxin B interacted with the polar and nonpolar regions of the phospholipid, while gramicidin S interacted only with the polar region. The implication of these observations with respect to lipid–protein interactions and

antibiotic activity was discussed (898). At equimolar concentrations, chlorothricin formed a strong complex with lecithin and prevented the phospholipid from swelling in water. This was ascribed to nonpolar association of the antibiotic with the hydrocarbon chains of the phospholipid (899). Phospholipid, cholesterol, protein, and mixed lipid–protein monolayers were used as models to study interactions between 3,4-benzpyrene, a carcinogenic hydrocarbon, and cell membranes. The carcinogen was shown to interact strongly with phospholipid, protein films, and mixed lipid–protein films. The biological significance of these data was discussed (900). A similar study dealt with interactions between dimethyl sulfoxide and these monolayer model films. The results indicated that the remarkable penetration abilities of dimethyl sulfoxide may be due to some alteration of protein structure as a result of dehydration at the biomembrane (901). The interactions of some oral contraceptive steroids with cholesterol and lecithin monolayer films were studied to determine their role in platelet aggregation. The data support the hypothesis that steroids may adsorb at platelet surfaces and alter the surface properties or the penetrability of the platelet membrane to cause increased platelet aggregation (902).

Additional references pertaining to interactions of drugs with biological substances are given in Table XXVI.

Interactions of Drugs with Nonbiological Substances— A theoretical study dealt with the calculation of heats of complexation and the structures of charge-transfer complexes of chloranil, fluoranil, and tetrachlorophthalic anhydride with various methylbenzenes in carbon tetrachloride solvent. The theoretical interaction energies were calculated from the monopoles-bond polarizabilities approximation, and the ground-state charge distributions were taken from CNDO/2 calculations[1]. The solvent contribution to the heat of complexation was estimated using the cavity model (927). The effects of water on the charge-transfer transition energy and the equilibrium constant were investigated for complexation of chlorpromazine hydrochloride with *p*-xyloquinone and of sodium *N*,*N*-dimethyl-*p*-aminobenzoate with sodium anthraquinone-2-sulfonate (928). In a subsequent study, the influence of water on the rate of charge-transfer interaction between aniline and chloranil was reported. It was concluded that water promotes the charge-transfer complexation presumably due to the enhancement of the solvent polarity (929).

Metal complexes of thiouracils were studied by potentiometric titration and polarographic techniques in an attempt to determine stability constants and rationalize the mechanistic bases of the relative complex stabilities, thiouracil structures, and biological activities. The relative tendency of metal ions to complex with thiouracils, $Cu^{+2} \gg Pb^{+2} > Cd^{+2} \gg Ni^{+2} \sim Zn^{+2}$, was found consistent with the "natural order" of such transition metals, their relative ionic radii, their electronic structure, and the concept that "soft acids" prefer to complex with "soft bases" (930). Stability constants were determined for a series of imidazole, pyrimidine, and related heterocyclic thiones with Cu^{+2}, Al^{+3}, and Fe^{+3} ions. The relative magnitude of these constants indicated formation of four-membered chelate rings involving nitrogen and sulfur atoms (931). Metal complexes of *ortho*-, *meta*-, and *para*-aminobenzoic acids were examined by atomic absorption, IR, differential thermal analysis, and thermal gravimetric analysis techniques. These complexes consisted of 2:1 ratios of metal to ligand, with amino and carboxyl groups assumed to participate in the complex formation (932). Based on electron microscopy and gel chromatography studies of an iron–dextran complex, a structural model was presented for the complex, with dextran attached by the terminal metasaccharinic acid units to the FeOOH component (933).

The interactions of alkyl trimethylammonium bromides with amaranth were investigated by microscopy, microelectrophoresis, phase solubility, and other physi-

[1] Complete neglect of differential overlap/second parameterization.

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

Reference	Topic
903	Review of the binding of iodinated radiocontrast agents to blood plasma proteins
904	Review of drug binding to plasma proteins
905	Review of drug binding to plasma and tissue proteins, encompassing influence of physicochemical properties of drug on binding and methods for protein-binding study
906	Review describing biological role of metal complexes with drugs and their effects on membrane permeability
907	Review of drug interactions with nucleic acids, proteins, and membranes studied by fluorescence spectroscopy
908	Binding of phenothiazines to bovine serum albumin and related phenomena
909	Binding of ^{99m}technetium to human serum albumins
910	Binding of sulfobromophthalein (bromsulphthalein) sodium by human serum albumin
911	Binding of pentylenetetrazol to plasma proteins
912	Binding of edetate (EDTA), histidine, and aspirin (acetylsalicylic acid) to zinc–protein complex in intestinal content, intestinal mucosa, and plasma
913	Binding of aluminum by hair shown as diffusion control process, with activation energy of 11 kcal. mole^{-1}
914	Protein binding of nikethamide (cordiamine) as reason for its action on tissue respiration processes
915	Niacin (nicotinic acid) bound to human proteins in amounts of 20.1% to α-globulin, 17% to γ-globulin, 5.3% to albumin, and 2.6% to β-globulin
916	Interaction of penicillin and tetracycline with microbic polysaccharides
917	Dermal binding of testosterone and benzyl alcohol to human autopsy skin, and its significance to percutaneous absorption
918	Effects of dilution, specific ions, and inhibitors on thyroxine binding of serum proteins
919	Fluorescent dye 1,8-anilinonaphthalenesulfonate competition with thyroxine for binding to globulin
920	Tetracycline–bovine serum albumin interactions with 2–3 kcal. mole^{-1} enthalpy change seeming to involve formation of noncovalent bonds
921	Relation between the structure of tetracycline derivatives and the extent of binding to albumin
922	Reversible binding of oxacillin, nafcillin, and cephalothin to human serum protein
923	Complexation of chlorpromazine with adenosine and adenosine phosphates
924	Extent of *in vitro* plasma protein binding of amphetamine in different species found independent of drug concentration, similar in normal and uremic plasmas, and significantly different among the species
925	Binding of amobarbital, phenobarbital, and pentobarbital to human serum albumin at various pH's
926	Binding of phenylbutazone and sodium warfarin to bovine serum albumin

cal techniques. The dye–surfactant complexation was shown to be a coacervation phenomenon, and the results were interpreted using general coacervation theories (934). Crystalline 1:1 complexes of acetaminophen with caffeine and theophylline were isolated from aqueous solution. The caffeine–acetaminophen complex was found to exist in three forms, each differing only in the degree of solvation (935). Acetaminophen was shown to form a stable 1:1 complex with antipyrine; the complexation involved amino and hydroxyl groups of acetaminophen and the carbonyl group of antipyrine (936). The formation of a complex between phenylmercuric nitrate and sodium metabisulfite, which is more active in acidic media but less active in alkaline media than phenylmercuric nitrate alone, provided an explanation for the observed antibacterial activity of the drug–metabisulfite mixture (937). A series of six 2,6-diamino-8,9-disubstituted purines was shown to form cyclic 2:1 hydrogen-bonded complexes with phenobarbital in dilute chloroform solution at room temperature, whereas 9-phenbutyladenine formed a 1:1 complex with phenobarbital under similar conditions (938). The effects of the CNS active drugs pentobarbital, bemegride, and trimethadione on the NMR spectrum of formanilide showed that the *cis*-isomer of the amide forms a doubly hydrogen-bonded complex with the drugs, but the *trans*-isomer favors formation of a single hydrogen bond. Implications of results in terms of the mechanistic basis of CNS active drugs were discussed (939).

The formation of inclusion complexes of barbiturate drugs with cycloheptaamylose was examined by solubility analysis and by circular dichroism measurement. These complexes existed in 1:1 ratios with the relative strength of interaction in the order: phenobarbital > pentobarbital > amobarbital > barbital (940). The interactions of β-cyclodextrin with six barbituric acid derivatives and thiopental were studied by solubility analysis. Barbituric acid derivatives having a cyclic substituent at the 5-position formed a more stable complex than those having an acyclic substituent. The physical stability of aqueous solutions of sodium barbiturates was improved in the presence of β-cyclodextrin (941).

The interaction of sodium lauryl sulfate with polyvinylpyrrolidone and polyvinyl alcohol in aqueous solutions was studied by intrinsic viscosity and membrane equilibrium measurements. The intrinsic viscosity and membrane equilibrium yielded a bell-shaped profile with increasing concentration of sodium lauryl sulfate (942). It was shown that monolayers of polyvinylpyrrolidone copolymers interact more strongly with dissolved benzoic acid than with *p*-hydroxybenzoic acid. However, in bulk solutions of polyvinylpyrrolidone, the latter is more strongly bound. This difference was ascribed to the highly oriented structure which polymers assume at interfaces (943). Aqueous mixtures of papaverine hydrochloride and atropine sulfate with various surfactants and polymer excipients were examined by TLC. An interaction between the drugs and sodium lauryl sulfate, as well as a tendency toward complexation of the drugs with methylcellulose, was evidenced (944). Equilibrium constants and coordination numbers were determined for complexes obtained by coupling methacrylic acid and acrylic acid polymers with various ammonium salts of drugs. The experimental data were interpreted by a modified Bjerrum-Gregor theory (945). Complexation of aspirin, salicylic acid, and thimerosal with methacrylate copolymers was indicated by equilibrium dialysis measurements (946).

Additional references related to interactions of drugs with nonbiological substances are listed in Table XXVII.

Table XXVII—Additional References on Interactions of Drugs with Nonbiological Substances

Reference	Topic
947	Review of interactions of diphenylhydantoin, phenobarbital, and other antiepileptics with other drugs of various activities
948	Complex formation between nicotinic acid diethylamide and sulfanilamide and the solubility function of the 1:1 complex in water and acetone
949	NMR studies of interactions between oxyethylene–oxypropylene, macrogol, and phenol
950	Intramolecular hydrogen bonding in pamaquine studied by fluorescence spectroscopy
951	Aggregation of (+)-propoxyphene hydrochloride in aqueous solution examined by circular dichroism measurements
952	Reversible thermal aggregation of vinblastine sulfate and its interactions with hydrophobic groups
953	Ionic associations of amphetamine isomers with mandelic and tartaric acids studied by conductometric measurements
954	Molecular associations of amphetamine isomers with optically active and racemic acids studied by thin-layer electrophoresis
955	Association of tetracycline ions in solution and in complexes with polyelectrolytes
956	Stability and solubility of tetracycline complexes with pyrocatechuic acid and gentisic acid determined as a function of pH
957	Association constants of 14 aminoketones with phenol and their biological activity
958	Amines capable of forming dissociable complexes with aldehyde group of pyridoxal postulated to have radioprotective activity
959	Binding of metal ions and aspartic acid measured by electric conductivity found to decrease in the order of magnesium, calcium, strontium, and barium
960	Structure and bonding of water molecules in α-cyclodextrin hexahydrate
961	Survey of interactions between surfactants and macromolecules (proteins and polymers)
962	Interaction between dextroamphetamine sulfate and spray-dried lactose in solid–solid mixture studied by diffuse reflectance spectroscopy
963	Solid–solid interaction between sulfamethoxazole and lactose examined by thermal analytical methods

Surface Phenomena—The publications dealing with surface phenomena are divided into four major categories: interface studies, adsorption studies, general properties of surfactants, and micelle studies. However, because of the obvious overlap among these categories, the reader with a special interest in this field is advised to consider the entire section.

Interface Studies—Equations correlating the free volume and zero energy of interaction with the surface tension of liquids are based upon the assumption that each particle moves independently in its potential well. Since this concept does not account for the interaction resulting from particle oscillation, the free volume term in these equations was replaced by the free phase space, which can be calculated from the free energy and entropy of interaction among particles (964). Surface tension calculation for simple liquids using the Kirk-

wood–Buff theory, assuming a smooth variation of density between liquid and vapor, and the estimation of the thickness of the interface were shown to be in fair agreement with experimental results (965). The surface energy, surface entropy, and latent heat of surface formation were calculated for water, benzene, *n*-butanol, and six other similar liquids from the information on surface tension as a linear function of temperature (966). The surface tensions of oleic acid, sodium oleate, and a mixture of both in aqueous media were determined as a function of temperature and concentration. Occurrence of intermolecular attraction between these compounds was indicated from the surface energies calculated for the mixture (967). A thermodynamic description of the interfacial layers was presented by treating interfacial layers as a collection of molecular planes (968). This model, at equilibrium, was shown to be in agreement with the Gibbs formula (969).

The thermodynamic properties of the film compression process were evaluated for a series of liquid-condensed and liquid-expanded lipid films. It was shown that, for the liquid-condensed and liquid-expanded monolayers, the hydrocarbon region is energetically similar to bulk hydrocarbon liquids. Entropies of compression for the polar groups suggested that characteristic changes in water structure are likely to occur in the formation of each condensed monolayer state (970). In a subsequent study with mixed lipid films, it was concluded that: (*a*) in the absence of specific interactions, the liquid-condensed films of octadecanol, stearic acid, and dipalmitoyl lecithin are immiscible with cholesterol; and (*b*) cholesterol forms nonideal mixtures with liquid-expanded lipid films (971). Surface pressure–area curves were obtained for mixed monolayers of myristic acid, an expanded film-forming acid, with condensed film-forming acids of chain lengths from C_{17} to C_{26}. The change in characteristics of the curves with chain length indicated the dominant effect of hydrophobic interactions (972). An empirical equation was given relating the average carbon chain length of a molecule in films spread at the air–water interface with the pH of the aqueous phase, and it was applied for films of palmitic acid, stearic acid, arachidic acid, and behenic acid (973). Measurements of equilibrium spreading pressure for various saturated fatty acid triglycerides revealed that the spreading pressure decreases while the collapse pressure increases with the increase in fatty acid chain length. Successive stages leading to collapse of the film were discussed (974). IR spectra of stearic acid films spread on aqueous aluminum chloride solutions were studied by the attenuated total reflectance (ATR) technique to correlate the molecular structure of the film with the film stability. The stability of this film was attributed to the formation of an adsorption layer of dihydroxoaluminum stearate (975).

The surface pressure–area and oxygen permeation behavior of stearic acid, dipalmitoyl lecithin, and lung alveolar surfactant films were investigated to elucidate the mechanism of surface hysteresis exhibited by the lung surfactant. Mechanisms for the hysteresis phenomenon were proposed based on surface relaxation and compression rates of these films. The results of oxygen permeation studies indicated that only the films with the abilities both to pack efficiently in the condensed state and to regenerate themselves from the collapsed state significantly reduce oxygen permeation (976). The interaction of cetyl sulfate and cetrimonium (cetyltrimethylammonium) ions with dipalmitoyl glycerol monolayers at the air–water interface was followed by variation of the surface pressure and surface potential. The kinetics and mechanism of these monolayer interactions and their implications to microstates of biomembranes were described (977). The free energy changes, activation energies, and activation entropies associated with material transfer through liquid–liquid interfaces were experimentally determined for propionic acid, *n*-butyric acid, and *n*-valeric acid in the benzene–water system. The increase in the interface resistance with increasing alkyl chain length was attributed to the change in activation entropy (978). Thermodynamic parameters for the transfer of *n*-alkanols at the air–solution interface were obtained from surface pressure measurements. In accordance with Traube's rule, free energy values decreased linearly with increasing alkyl chain length and the enthalpy values were independent of the chain length. Approximately a twofold difference was observed between the theoretical and experimental entropy values and was presumed to be due to hydrogen bonding between alcohol and water (979). Equations were derived characterizing diffusion and viscous-type propagation of a liquid on solids (980).

Additional references on interface studies are listed in Table XXVIII.

Adsorption Studies—Gibbsian thermodynamics of adsorption from liquid mixtures on solids were formulated in terms of excess properties. A general expression was derived for the temperature coefficient of the surface excess in terms of heat of immersion of the adsorbent. Experimental data on nonisothermal adsorption and the heats of immersion were reported for the benzene–cyclohexane system adsorbed on silica gel (1001). A new isotherm for adsorption of a monolayer on a smooth surface, which is reducible in limiting cases to the Langmuir, Freundlich, or Temkin isotherm, was proposed. Immobile and mobile adsorbed molecules were considered, the number of the latter being determined by a Boltzman expression (1002). The influence of counterion concentration on the thermodynamic parameters of dodecylpyridinium chloride at the free surface of solution was investigated. The free energy, enthalpy, and entropy of adsorption values were correlated with the temperature and counterion concentration of the solution (1003). Adsorption of five steroids was determined at the oil–water interface in an effort to test a localized and a nonlocalized model for the adsorbed layer. Since neither model provided an accurate description of the adsorption kinetics, it was concluded that both the energy barrier and diffusion play a role in adsorption kinetics (1004).

Carstensen and Su (1005) described the effect of solvent intercalation in adsorption isotherms of montmorillonite from solvents with a high dielectric constant. It was shown that the number of solvent layers in the interlaminar spacing is higher when the clay is equilibrated with liquid than with the solvent vapor. These

Table XXVIII—Additional References on Interface Studies

Reference	Topic
981	Review describing effective surface-layer thickness, thermodynamics of surface phenomena, surface-layer thickness at two-phase boundary, *etc.*
982	Structural properties and biological significance of organic films; specific data for film structure of stearic acid esters
983	Review of the influence of interfacial tension-driven instabilities on rates of mass transfer in liquid–liquid systems
984	Review of the theory of heat of wetting and its application to solid surface studies
985	Review of structural theories of surface tension of liquids, with emphasis on molten salts
986	Comparison of liquid–liquid interfaces and solid–vacuum interfaces
987	Review of intermolecular energies in lipid monolayers, use of film balance for measuring thermodynamic properties of monomolecular films, FORTRAN computer programs, *etc.*
988	Review of surface and interfacial tension contact angle
989	Surface tensions of organic solids—amides, substituted acids, quinones, caffeine, and camphor
990	Contact angle and wettability of packaging materials and of human skin
991	Autoxidation of cholesterol in aqueous dispersions and in monomolecular films
992	Description of nondifferential equations relating surface tension to concentration, temperature, and other properties that depend on the size and energy characteristics of the particles
993	Surface pressure–area behavior of several fatty acid monolayers, dipalmitoyl lecithin monolayers, and mass transfer across a liquid–liquid interface
994	Equation involving cohesive force for the surface pressure of long-chain ampholytes at oil–water interface
995	Monolayers of poly(organosiloxane) on water; structure of siloxane skeleton without decisive influence on spreading phenomena
996	Dispersion forces and surface tension of liquids described in terms of cavity formation theory
997	Role of the diffusion layer in water-in-oil microemulsions; Adamson's model for microemulsions modified to allow for the diffusion layer in the aqueous droplet interior
998	Influence of surface area variation on kinetics of hydration of tricalcium silicate
999	Automated drop volume apparatus described for surface tension measurement
1000	Surface properties and intermolecular interaction in liquid media

authors (1006) also presented data supporting the hypothesis that the adsorption of unionized organic compounds on montmorillonite is a surface adsorption phenomenon mediated *via* an ion–dipole interaction. Dissolution and dialysis studies were reported showing that cationic drugs and some nonionic drugs adsorb very strongly to montmorillonite clay. A two-step process involving a cation-exchange reaction followed by strong surface chemisorption was proposed as the mechanism for cationic drug–clay binding. The initial urine levels of amphetamine after oral administration of the drug–clay complex were significantly lower than those for the pure drug (1007). The adsorption of benzidine on montmorillonite suspended in aqueous solutions was studied as a function of pH and electrolyte concentration. The interaction between benzidine and the clay was considered to be a cation-exchange process (1008).

The liquid and vapor phase adsorption of primary aliphatic alcohols (C_1–C_{10}) on calcium and sodium montmorillonite was investigated by X-ray techniques. Molecular configurations of the adsorbed molecules consistent with the experimental data were suggested (1009). The adsorption of salicylic and gallic acids by sodium and calcium forms of kaolinite, montmorillonite, and other clays was determined in aqueous media. The results were discussed in terms of the differing crystal structures of the clays (1010). In aqueous solutions, Langmuir-type isotherms were observed for the adsorption of crystal violet on the H-forms of bentonite and kaolinite. Both clays sorbed crystal violet in amounts greater than their cation-exchange capacities, indicating that unionized molecules of the dye were adsorbed in the interlamellar spaces of the clay and that dimerization of the dye occurred on the clay surfaces (1011). Adsorption of benzoic acid by kaolin was studied as a function of pH. For effective preservative action, when both benzoic acid and kaolin are present in a formulation, the use of either high benzoic acid concentrations at pH > 5 or low concentrations at pH < 5 was recommended (1012).

Adsorption of tetracycline on calcium fluoride was investigated in an attempt to develop a physical–chemical model capable of describing the adsorption of specific tetracycline species from aqueous solution onto model adsorbents, both in the presence and absence of added electrolytes and over wide concentration and pH ranges. In the absence of other electrolyte species, Langmuirian-type adsorption isotherms were observed when the equilibrium concentrations of the adsorbate were calculated to reflect the activity of the negatively charged tetracycline species. The data obtained in the presence of fluoride or sulfate anions were explained on the basis of competitive binding by these anions for the same surface site. In the presence of calcium or magnesium cations, it was proposed that other drug species adsorb simultaneously with the negatively charged tetracycline species (1013). Determination of adsorption isotherms for four sulfanilamides on activated carbon, as a function of pH, showed an adsorption maximum between pH 4.5 and 5.5, corresponding to the isoelectric points of the molecules (1014). The influence of surface area of activated carbon upon the adsorption of coccinine and picric acid from granular and other forms was investigated. A mathematical interpretation of the data showed that the adsorbing power of the carbon can be represented by an exponential equation (1015, 1016).

Additional references on adsorption studies are listed in Table XXIX.

General Properties of Surfactants—Surface activity and emulsifying properties of quaternary ammonium salts were correlated with the structure of the surfactant molecule and its orientation at the toluene–water interface. Differences between the predicted and experimental values of adsorption energies suggested that about 40% of the methylene groups present in the surfactant molecule were submerged in the aqueous phase. The maximum emulsifying ability was observed for the alkyl trimethylammonium-type compounds containing 14–16 carbon atoms (1031). The surfactant properties of a water-soluble phosphated nonylphenol ethoxylate in aqueous media were examined as a function of pH, temperature, and surfactant concentration. From the measurements of the CMC in buffer solutions

Table XXIX—Additional References on Adsorption Studies

Reference	Topic
1017	Review of adsorption properties of hydrophobic surfaces, including discussion of adsorbate interaction models and heats of adsorption
1018	Review of theories of monolayer adsorption, isoenergetic and homotactic adsorbents, and adsorption isotherms of simple molecules
1019	Review of ionic double layers and adsorption
1020	Diffuse reflectance spectra as a source of information about the absorption spectra of adsorbed molecules
1021	Adsorption kinetics at a solution–air interface of a surface-active substance
1022	Role of hydrophobic interactions during adsorption of simple diphilic molecules studied by the dependence of adsorption on temperature
1023	Adsorption of sodium and calcium lauryl sulfates at the surface of their aqueous solutions
1024	Heats of reversible adsorption measured for *n*-heptanol, *n*-nonanol, and secondary straight-chain nonanols
1025	Evaluation of sorption–desorption processes between polymers and low molecular weight compounds by GC
1026	Sorption of preservatives by plastic packaging materials relative to polarity of the plastic and the preservatives
1027	Adsorption of a nonionic surfactant on different clays limited by formation of a monomolecular layer
1028	Adsorption of sodium salicylate on clay minerals
1029	Possible use of Estonian clays in pharmaceutical preparations evaluated by their adsorption characteristics
1030	Adsorption kinetics of anionic surfactants at air–water interface in the presence of electrolytes

Table XXX—Additional References on General Properties of Surfactants

Reference	Topic
1046	Review of solubility and micelle formation properties of surfactants in nonaqueous solutions
1047	Review of solubilization properties of surfactants in nonaqueous solutions
1048	Review of physicochemical properties of polyoxyethylene alcohols
1049	Review of application of surfactants to improve drug yield and formulation stability
1050	Review of surfactant classification and selection, emulsion polymerization, and surfactant coating problems
1051	Review of properties, classification, evaluation, industrial application, *etc.*, of nonionic surfactants
1052	Review of physical properties of surfactants including surface tension, film formation, micelles, HLB, and rheological properties
1053	Review discussing concept of HLB, coalescence of emulsion particles, and partition coefficient of surfactants in terms of chemical potential
1054	Review of characteristics of oil-soluble surfactants in nonaqueous media, solubilization
1055	Review describing effects of chain length and branching in sodium alkyl benzenesulfonate surfactants upon their interfacial properties
1056	Review of relations between chemical structure and surface activity discussed in terms of mechanism of surface activity, role of different functional groups, molecular configuration, and chain branching
1057	Interfacial activity of sodium lauryl sulfate in the presence of alcohols and its effect on emulsion stability
1058	Influence of surfactants on liquid absorbability of various powders of pharmaceutical interest

over the 4.0–9.2 pH range, it was suggested that the surface-active properties of the compound were unaffected by the state of ionization of the polar phosphate group. The group interfacial cross-sectional area of the molecule varied from about 0.92 nm.^{2} at 15° to 0.82 nm.^{2} at 50°, which was consistent for the system having nonionic portions of the molecule oriented at the interface (1032). A thermodynamic treatment for the occurrence of a minimum on the surface tension isotherm suggested that the presence of an impurity that lowers the CMC causes a minimum on the isotherm, but an impurity that increases the CMC may not always yield a minimum (1033). The literature data for surface pressures of mixtures of anionic and cationic surfactants were found consistent with theoretical predictions based on the surface behavior of the separate constituents (1034). An ultrasound method was described for the determination of the degree of hydration of nonionic surfactant molecules in an aqueous solution (1035).

The association equilibrium and micelle formation by polyethylene glycol *n*-nonylphenyl ether (1036) and β-D-*n*-octyl glucoside (1037) were determined by vapor pressure, osmometric, light scattering, ultracentrifugation, and sedimentation methods. For both surfactants, the data agreed with the model of closed association, and a linear relationship existed between the enthalpy and entropy of association. A subsequent publication dealt with the theoretical estimation and experimental measurements of viscosity of the two surfactants (1038). The effects of a polymer interacting with a surfactant upon the solubilization of the surfactant, surface tension, and viscosity were discussed. Interactions of polymers were more pronounced with anionic surfactants than with nonionic and cationic surfactants (1039). In a similar study, viscometric and conductometric measurements showed that the interactions of polyvinyl alcohol with anionic surfactants occurs below the CMC's (1040).

The HLB values of fluorocarbon and ionic hydrocarbon surfactants were related to their CMC values. A modified equation, derived from Davies' theory, was employed for the estimation of cohesive free energy change per methylene group in the surfactant molecule (1041, 1042). Application of NMR as a direct measure for the determination of HLB values for nonionic surfactants was demonstrated. Estimation of the relative proportion of lipophilic and hydrophilic protons by this technique provided the basis for the calculation of the HLB characteristics of a surfactant (1043). The HLB values of surfactants were correlated with the ratio of the work of surfactant adsorption from two liquid phases at their interphase (1044) and with the spreading coefficient determined from surface and interfacial tension measurements (1045).

Additional studies on general properties of surfactants are listed in Table XXX.

Micelle Studies—The definition and phenomenological interpretation of the CMC in multicomponent systems were discussed. The CMC was considered as the transition point for a second-order phase transition in a multicomponent system. Expressions were given for the mutual dependencies of temperature, pressure, and composition of a system at its CMC (1059). Mukerjee (1060) applied procedures for dealing with multiple

equilibria in stepwise self-association when all species are in a rapid association-dissociation equilibrium to micellar systems. The possibility of determining the number average degree of association by utilizing experimental weight average values was demonstrated. The self-association model, along with some approximate nonideality corrections, was stated to reproduce the shapes of some observed reduced turbidity data showing minima (1060). A model describing the kinetics of micelle formation from chemical relaxation studies predicted a single relaxation time and a correlation between the relaxation time and overall surfactant concentration. The model, consisting of an associated state of micelles of various sizes and a nonassociated state of monomers, assumed that the enthalpy change for the micellization was independent of the size of the micelle (1061). Some consequences of the equilibrium model of closed association between monomeric and polymeric molecules for micellar systems were discussed. In some cases, the Debye method of determining monomer concentration suggested the existence of a premicellar equilibrium (1062).

The changes in molecular motion of ions and their hydration layers during adsorption from the bulk solution into the Stern layer of a detergent micelle were studied by NMR. The results suggested that the rate of rotation of hydrated sodium ions is unlikely to alter by >35% on adsorption from the bulk to the Stern layer of sodium lauryl sulfate micelles; however, the symmetry of the hydrated layer may be altered by the charged head groups of the micelle (1063). The kinetics of micelle dissociation determined by temperature-jump and NMR methods did not agree with the mechanism involving a single, slow step dissociation process. The results, when treated on the basis of many sequential steps for dissociation, were compatible with rate constants 10^5–10^6 $sec.^{-1}$ for micelles having aggregation numbers greater than 50 (1064).

Yalkowsky and Zografi (1065) calculated the partial molal volume of a large number of surfactants in the micellar state by adding partial atomic values and accounting for the hydrocarbon liquid-like nature of the micelle interior. This approach provides a means of determining relatively accurate values by simple calculation (1065). In response to a previous publication questioning the existence of spherical-shaped micelles of common single-chain surfactants, Zografi and Yalkowsky (1066) concluded that the exact shape of micelles is still an open question but, in general, previous arguments presented against the spherical micelle shape were considered invalid. The authors proposed that until more definitive evidence is available, a spherical or near-spherical micelle model can be considered useful in the estimation of molecular area and other micelle dimensions. Tanford (1067) concluded, on the basis of simple geometric considerations, that most of the common small soluble micelles must be ellipsoidal rather than spherical in shape. It was suggested that amphiphiles with a single hydrocarbon chain per polar head group form micelles with a distribution of sizes with spherical and ellipsoidal shapes, while those with two hydrocarbon chains per head group prefer extended bilayer or vesicle-shaped micelles.

The number average micellar molecular weight for a purified sample of polysorbate 80 in aqueous systems was determined by membrane osmometry. This method was also employed to study the effect of micellar solubilization on the molecular weight of the micelle (1068). The surface tension measurements of aqueous polysorbate 20 solutions from 0.001 to 10 mg./ml. concentrations suggested that the CMC of polysorbate 20 is in the vicinity of 0.06 mg./ml. surfactant concentration (1069). The CMC of homogeneous polyethylene glycol lauryl ethers was determined from the spectral change produced by the charge-transfer solubilization of 7,7,8,8-tetracyanoquinodimethan. The values obtained by this method were consistent with those obtained by surface tension measurements (1070). The aggregation of an uncharged surfactant in aqueous solution was described in terms of a multiple equilibrium model. Average aggregation numbers and diffusion coefficients for *n*-alkyl hexaoxyethylene glycol monoethers were calculated from light scattering and free boundary experiments (1071).

The temperature dependence of the CMC of several cationic surfactants in the presence of glucose or sucrose was reported. Thermodynamic parameters were calculated using the uncharged phase-change model. The changes in CMC values in glucose or sucrose solutions were interpreted as the effects of modifications in water structure and the reduction of dielectric constant (1072). Micellization behavior of four antihistamines in aqueous solutions was studied by light scattering to estimate the effective micellar charge, CMC, and degree of ionization. It was pointed out that since the effective charge refers to the equivalent charge under ideal conditions, which is generally lower than the true value at the shear surface, the value for the degree of ionization, therefore, is likely to be an underestimation of the extent of ionization of the micelles (1073). Aggregation numbers and effective charges of two cationic surfactant micelles were determined at various ionic strengths and temperatures. From the micellar parameters, the hydrophobic and electrostatic contributions to the free energy and enthalpy of micellization were calculated and the enthalpy values were compared with calorimetric values (1074).

Additional references on micelle studies are given in Table XXXI.

Dispersion Stabilization—The quantitative investigation of coalescence kinetics in dilute oil-in-water emulsions was presented. Experimental data were in agreement with the flocculation model, but they significantly deviated from the classical coalescence model. However, incorporation of the hydrodynamic effect into the coalescence model yielded reasonable agreement between the experimental coalescence data and the theoretical results (1089, 1090). The effect of nonlagging molecular forces on the coagulation and condensation growth of highly dispersed aerosol particles was studied as a function of the size of the impinging particles. It was shown that molecular forces have less effect on coagulation of particles of different sizes than of identical sizes (1091). The changes in interfacial tension, particle size, and stability of an oil–water–nonionic surfactant emulsion system were studied as

Table XXXI—Additional References on Micelle Studies

Reference	Topic
1075	Review of micelle formation of surfactants
1076	Review of micellization of surfactants in nonaqueous solutions
1077	Review of CMC, size, shape, and solvation of micelles
1078	CMC determination of nonionic surfactants by interference refractometry
1079	Decrease in CMC of polyethylene glycol alkyl ethers with increasing hydrocarbon chain; increase in CMC with increasing number of oxyethylene groups
1080	Surface tension, conductivity, and CMC data for aqueous rifamycin SV solutions
1081	Use of electron spin resonance (EPR) spectra for estimation of the local counterion concentrations at the micellar surface of copper lauryl sulfate
1082	Fluorescence absorption and emission studies of solubilization of pyrene in long-chain cationic micelles
1083	Second CMC of the aqueous solution of sodium lauryl sulfate shown by conductivity studies
1084	Polarographic determination of CMC of anionic surfactants
1085	Effect of temperature on the CMC of decylpyridinium chloride
1086	Degree of dissociation and CMC of some cationic surfactants
1087	Micelle formation of sodium lauryl and sodium tetradecyl sulfates in water–organic solvent mixtures evaluated by conductivity and viscosity measurements
1088	Influence of polar additives (*e.g.*, caproic acid, hexanol, and aniline) on CMC of sodium alkyl phosphonates

functions of temperature and ethylene oxide units of the surfactant. In systems containing surfactants with more than 10 ethylene oxide units, the particle size was decreased and the stability improved with increasing emulsification temperature (1092). The factors influencing coalescence in liquid–liquid dispersions, including the effect of mass transfer, shape of droplets, agitation, and coalescence at a liquid or solid surface, were discussed (1093).

Expressions for the work and heat of wetting were derived and applied to heptane–water–powdered glass systems containing variable amounts of a surface-active agent (1094, 1095). Addition of lauryl alcohol to a mineral oil (Nujol) oil-in-water emulsion had a stabilizing effect, while the stability of an olive oil-in-water emulsion was unaffected by the addition of lauryl alcohol. These observations were explained in terms of adsorption of lauryl alcohol at the mineral oil–water interface (1096). The effect of micelle formation and the nature of the oil phase on the distribution of a nonionic surfactant in three- and four-component emulsions was investigated. The results were related to mechanisms responsible for the formation and stability of emulsions (1097). The stability of a liquid petrolatum–water emulsion containing 0.2% sodium lauryl sulfate decreased upon storage up to 25 days and thereafter increased with time. This was rationalized in terms of an initial desorption of the surfactant upon increase in the droplet size, followed by readsorption of the surfactant at the oil–water interface (1098). The stability and phase dispersion of petrolatum emulsions were studied as functions of surfactant and water concentrations. The stability was enhanced by increasing the proportion of water, while the stability was not greatly influenced by the surfactant concentration (1099).

The role of adsorption in the interaction of water-soluble polyelectrolytes with colloids and highly dispersed systems was discussed. The reversible adsorption was considered as an important phenomenon governing stability of relatively dilute systems, while irreversible adsorption causing alteration of the solid surface was considered important in the stabilization of concentrated dispersions (1100). Theoretical calculations analyzing the effect of polydispersity of nonattracting spherical particles upon sedimentation volume were presented. In a polydisperse mixture, small particles occupy interspaces between large particles so that the sedimentation volume becomes smaller than for a monodisperse mixture (1101). The colloidal stability of polydisperse systems was calculated for particles differing in size and surface potential. According to these calculations, dispersions of particles with Gaussian distributions of radii or surface potential were shown to be less stable than the corresponding monodisperse systems with constant surface potential (1102). An asymptotic solution to a simplified equation for the kinetics of coagulation was applied to aerosol systems. The simplified coagulation model with a constant collision parameter was shown to approach a self-preserving form, which is independent of the initial distribution (1103).

Sedimentation kinetics of flocculated silica suspensions were studied to elucidate the role of ζ-potential in sedimentation mechanisms. In the initial time periods, the sedimentation rate constant was shown to be a function of both Stokes and aggregational forces; in the final phase, the reciprocal of the smaller of the two contraction rate constants was linearly related to the reciprocal of the ζ-potential (1104). The structural stability of montmorillonite and palygorskite suspensions in organic liquids was studied in relation to their electrokinetic properties. No direct correlation between the ζ-potential and stability of these suspensions was observed (1105). A kaolin suspension containing sodium caprylate was stabilized by the addition of caprylic acid. A phase diagram was presented for the water–sodium caprylate–caprylic acid liquid crystal system (1106). The effect of pH on the flocculation of bentonite sols by an acrylamide–acrylate copolymer was studied. The results demonstrated the existence of a flocculation threshold at the pH where the macromolecular chain exists in the completely extended form (1107).

Additional references on dispersion stabilization are given in Table XXXII.

Rheology—The structure and rheological properties of emulsions stabilized by the mixed emulsifier, polyethylene glycol 1000 monocetyl ether (cetomacrogol 1000) and cetostearyl alcohol, were investigated. The mixed emulsifier exhibited a self-bodying network phenomenon showing an increase in consistencies with increasing emulsifier concentration and with increasing temperature up to a maximum. At higher temperatures, consistency decreased as the network weakened and finally dissolved to form an isotropic solution. The mechanisms responsible for the formation of nonionic

Table XXXII—Additional References on Dispersion Stabilization

Reference	Topic
1108	Review of the behavior of colloidal particles in the presence of ions, surfactants, polyelectrolytes, and polymers
1109	Review describing current state of colloid science and areas of future research
1110	Review of the theory of lyophobic colloid stability
1111	Review describing force constants for molecular interactions involving hydrophobic surfaces
1112	Review of theories of dispersion and emulsion stability in nonaqueous media
1113	Review of ζ-potential, electrical double layer, and measurements of electrophoretic mobilities
1114	Analogy between Smoluchowski's equation for slow coagulation and Bhattacharya's equation
1115	Kinetics of emulsion stability dependent on the size of the dispersed phase
1116	Effect of electrolytes on the stability and breaking of emulsions
1117	Thermal transport process shown as major factor in the attenuation of sound in suspensions and emulsions
1118	Electrical interaction of colloidal particles with surface charge of constant density
1119	Flocculation and dispersion stability of mineral particles in relation to ζ-potential
1120	Physical structure of foam, and role of adsorption in foam stability
1121	Temperature stability of silver iodide and antimony sulfide hydrophobic sols stabilized by water-soluble polymer additives
1122	Theory of flocculant systems, and contributions of electrostatic and nonelectrostatic forces in relation to flocculation by water-soluble polymers
1123	Review of mechanism of solid suspension flocculation by synthetic polymers

networks were discussed and compared with mechanisms that function in gels formed by ionic surfactant–long-chain alcohol mixed emulsifiers (1124, 1125). The rheological behavior of 20% water-in-oil emulsions and dispersions of glyceryl tristearate crystals in oils was interpreted by the network model for a system of dispersed particles where particles tend to aggregate into random chains due to van der Waals' forces (1126). Rheological parameters were correlated with stability of liquid paraffin emulsions prepared with carboxymethylcellulose and with a mixture of gum acacia and gum tragacanth. The thixotropy of the carboxymethylcellulose preparation was practically constant during storage, while that of the gum emulsion increased and then decreased (1127). A similar study dealt with the rheological aspects of liquid paraffin, castor oil, and cod liver oil emulsions prepared with acacia and methylcellulose (1128).

The effect of wetting and surface-active agents on the rheological properties of various ointment gels was studied. Viscosity varied inversely with the degree of wetting, especially upon addition of surface-active agents (1129). Some rheological properties of hectorite dispersions such as viscosity, plastic flow, and static yield values were related to the particle shape, particle interactions, and addition of uni-univalent electrolytes (1130). Some anionic surfactants were found to increase the viscosity of the salicylic acid–cetrimide system to a maximum and then decrease it on further addition of the surfactant. The results were explained in terms of interaction between the anionic surfactant and free cetrimide molecules (1131). Quantitative measurements

Table XXXIII—Additional References on Rheology

Reference	Topic
1135	Review describing behavior in combined shear and electrical fields of dispersions, emulsions, polymer suspensions, *etc.*
1136	Review of rheological properties of monomolecular films—basic concepts and experimental methods
1137	Review of rheological properties of monomolecular films—experimental results, theoretical interpretation, and applications
1138	Elementary concepts of rheology relevant to food texture studies
1139	Rheological study of certain polyethylene glycol gels used in ointments
1140	Critical shear stress and estimation of the energy of contacts in lyophilic dispersed gelatin gel systems
1141	Interfacial shear viscosity at fluid–fluid interfaces containing surfactants or macromolecules
1142	Kinetics and mechanism of thixotropy of aqueous bentonite suspensions
1143	Surface viscosity measurements by an improved rotational–torsion method
1144	Effect of nonionic emulsifiers on the structural rheological properties of gels
1145	Influence of metallic soaps on the rheological properties of lipophilic bases

of thixotropic characteristics by a weight-actuated viscometer were demonstrated. This approach eliminated the problems involved in obtaining the classical hysteresis loop, since it provided data on the actual rates of breakdown and buildup of the systems (1132). Elastic, retarded elastic, and viscous components of the total deformation of gels were derived by plotting the penetration of a cone against the logarithm of time. The results were in agreement with those obtained from creep measurements with coaxial cylinders (1133). Rheological properties of Newtonian (silicone) fluids and a viscoelastic material (cetrimide cream BPC) were studied by a modified single-pan chemical balance method. Equations were given for the calculation of viscosities and compliances using this method (1134).

Additional references on rheology are provided in Table XXXIII.

PHARMACEUTICAL ASPECTS

Antibiotics—Water-soluble polymer derivatives of penicillin with vinylpyrrolidone copolymers were prepared. These derivatives retained their antimicrobial activity and were inactivated by penicillinase at a slower rate than penicillin (1146). Studies on combined precipitation of nystatin with polyvinylpyrrolidone from dimethylformamide solution included dynamics of precipitation, solvent effects, and the composition of the complexes (1147). Gramicidin was shown to aggregate in aqueous solution and form monolayer films at the air–water interface. The observed first-order rates of lecithin monolayer penetration by gramicidin were consistent with the proposed intramembrane dimerization of gramidicin to form ion-conducting channels (1148). Semipermeable membrane sacs containing *E. coli* were placed in the peritoneal cavity of rabbits to study the effects of proteins on the antibiotic activity of gentamicin. It was concluded that the serum protein inhibited, while immune serum enhanced, the action of gentamicin (1149).

Table XXXIV—Additional References on Pharmaceutical Aspects

Reference	Topic
	Antibiotics
1159	Review of chemical properties, pharmacokinetics, antibiotic activity, and clinical uses of erythromycin, oleandomycin, and troleandomycin
1160	Review of antimicrobial properties, pharmacokinetics, toxicity, and clinical uses of polymyxins, colistin, bacitracin, ristocetin, and vancomycin
1161	Review of erythromycin derivatives (esters, oximes, and quaternary salts) and their antibacterial activity
1162	Review of antibacterial activity and chemical stability of penicillin derivatives
1163	Review of biopharmacy of chloramphenicol
1164	Review of chemical and antimicrobial properties and mechanisms of action of streptomycin
1165	Review of mechanism of action, binding to ribosomes, and bacterial resistance of tetracycline analogs
1166	Effect of microbic polysaccharides and nonionic surfactants on the activity of some antibiotics
	Radiopharmaceuticals
1167	Review of radioactive compounds (*e.g.*, $^{59}FeCl_3$, insulin-^{131}I, and $Na_2{}^{51}CrO_4$) used in medical diagnosis
1168	Review of radioactive pharmaceuticals for medical diagnosis
1169	Review of therapeutic uses of radiopharmaceuticals
1170	Physical and biological half-life, radiation type, and purity of radiopharmaceuticals
1171	Preparation of high-purity carrier-free ^{123}I-iodine monochloride for iodination of radiopharmaceuticals

Heman-Ackah and Garrett (1150) reported on the effect of erythromycin on the action of lincomycin (phase II) and the 7(*S*)-chloro analogs of lincomycin against *E. coli*. Combinations of erythromycin and the 7(*S*)-chloro analogs of lincomycin demonstrated *a priori* antagonism of effects because of possible allosteric interactions which decrease the effects of one drug in the presence of the other at their site of action. It was emphasized that the dose–response relationship over a wide concentration range, as well as the kinetics and mechanisms of the separate drug action, must be considered in the quantification and prediction of combined action of antibiotics (1150). Addition of sodium edetate (EDTA) to sodium penicillin G or potassium phenoxymethyl penicillin (penicillin V) failed to enhance *in vitro* the antibacterial activity of either antibiotic against several bacterial species. Oral administration of edetate (EDTA) in combination with potassium phenoxymethyl penicillin or tetracycline hydrochloride also failed to increase antibiotic absorption in pigs (1151). Combinations of disodium carbenicillin and gentamicin showed an additive effect on *E. coli* and prevented its regrowth. Clinical use of this and other antibiotic combinations and development of resistance to these combinations were discussed (1152). An ophthalmic preparation of chloramphenicol containing methylcellulose remained in the conjunctival sac of the eye for several hours due to a viscosity effect, while one without the methylcellulose remained in the sac for only 10 min. (1153).

Radiopharmaceuticals—The type of theoretical background and practical experience required by a pharmacist in the preparation of radiopharmaceuticals in hospitals was discussed (1154). Pharmacological, pathological, and radiation hazards associated with the use of radioactive pharmaceuticals were reviewed. These hazards were considered slight with the use of modern radiopharmaceuticals, especially in view of their diagnostic value (1155). Factors influencing the stability of radioiodinated insulin including pH, concentrations of insulin and ^{125}I, and the addition of bovine serum albumin were examined. Insulin-^{125}I retained its immunoreactivity and gel filtration characteristics best when stored at <0.2 mcg./ml., −20°, in borate buffer (pH 8.6) with the addition of 1% bovine serum albumin (1156). Metal chelate complexes of ^{153}Sm and ^{169}Yb were prepared by exchange reaction for use as radiopharmaceuticals. Electrophoresis provided the most suitable method for controlling the radiochemical purity of the complexes (1157). Values for the equilibrium absorbed dose constants of ^{111}In and ^{169}Yb were calculated, and the metabolic behavior of indium and ytterbium chelates was reviewed (1158).

Additional references on pharmaceutical aspects are listed in Table XXXIV.

BIOPHARMACEUTICS

The various publications dealing with biopharmaceutics were subdivided according to the areas of special interest. However, because of the obvious overlap in subject matter, the reader seeking a thorough review should consider the entire section.

Current concern over generic inequivalence among various drug products was discussed by several workers (1172–1175). Smith (1176) stressed an urgent need to pursue clinical and pharmacokinetic measurements of relative absorption efficiency of those drugs where consistent potency is essential. Official action to introduce better *in vitro* standards and to implement quality control that will monitor any batch-to-batch variation in bioavailability was also recommended. Wurster (1177) discussed the influence of drug particle size, polymorphism, tablet hardness, formulation composition, dissolution rate, and other factors upon the efficacy of drug delivery systems. Similar aspects of factors influencing drug bioavailability were reviewed in several other publications (1178–1182).

An *in vitro* diffusion model for the transport rates of solutes in a three-phase system was applied to theoretical and experimental exploration of the pH–partition theory of drug absorption. Experimental rates for a variety of conditions reasonably correlated with computer predictions obtained by independent evaluation of physicochemical parameters in the system (1183, 1184). A three-phase model cell, employing a liquid lipid barrier, was used to establish correlations between reported *in vivo* absorption data and experimentally determined *in vitro* transport rates for a series of *N*-substituted heterocyclic sulfanilamides. These correlations suggested utility of this model to simulate passive drug absorption (1185).

Physical models for the diffusional transport of drugs across membranes of cells in culture suspensions were introduced by Ho *et al.* (1186) to describe the nature of the principal transport barrier, the kind of drug species

being transported, solute binding, and the effect of pH and partition coefficients on the drug transport. Mathematical expressions were derived for the quasi-steady-state diffusion through the membrane followed by distribution of drug in the heterogeneous cell interior (1186). A subsequent study dealt with the development of some baseline procedures for cell culture–drug transport experiments, consisting of cholesterol uptake by Burkitt lymphoma cells, and the methods of quantitative mechanistic interpretation of the experimental results (1187). A physical model for the adsorption of drugs applicable to situations in which the diffusional flux of the drug may be influenced by the bulk fluid flow and surface pH was described. Theoretical computations were made for different cases in simulation of the *in situ* absorption of drugs in animals with varying tonicity of the drug solution (1188). Previously reported results on human buccal absorption were quantitatively analyzed by the physical model approach using a two-phase compartmental diffusion model. Theoretical estimations of the absorption rate–buffer pH profiles were in good agreement with experimental results (1189).

A two-phase series model for the permeability behavior of the fully hydrated stratum corneum was examined using previously reported data on steroids. In general, reasonable self-consistencies were found among the various experimental results and parameters of the model (1190). Penetration of drugs through skin and the dependence of penetration rate on various parameters subject to vehicle influence were reviewed by Poulsen (1191). A systematic approach in the design of a topical corticoid dosage form, which provides good physical stability, patient acceptability, and optimum drug absorption through the skin, was presented (1192). Drug absorption through the stratum corneum of humans and the effects of hydration, temperature, humidity, solvents, and racial variations in drug penetration were reviewed (1193). The properties of the stratum corneum as a reservoir for topically applied drugs in humans were discussed. Data showing the effects of temperature and humidity on the reservoir content of topically applied sodium fusidate and fusidic acid were presented (1194). Application of the attenuated total reflectance IR spectroscopy technique to study the uptake of dodecylbenzenesulfonate by human skin *in situ* was demonstrated. The reproducibility of the technique was better than 5% for the drug permeation systems that are not influenced by moisture and/or hydrogen bonding (1195). General test methods for measuring percutaneous absorption of drugs in rabbits and guinea pigs were described, along with a discussion of various factors that affect percutaneous absorption (1196).

Engineering control systems analysis and optimization techniques were described for the evaluation and control of the therapeutic performance of drugs, drug products, and interacting drug combinations; for the design of dosage forms with optimum drug release patterns; and for setting optimum dosage regimens for individual patients. The feasibility of the approach was demonstrated by computer simulation of an ideally sought level of therapeutic drug response intensity (1197). A detailed basis for the use of experimentally determined dose–effect curves to transform observed intensities of pharmacological response into biphasic drug levels at all times following dosing by any route was presented. These principles were graphically demonstrated through the construction of dose–response–time surfaces (1198). An electronic circuit, which simulates theoretical curves associated with multiple-dosing kinetics, was described. Plasma level–time curves can be generated by this circuit, assuming a one-compartment open-model system and rapid intravenous injection (1199). A digital computer program was developed to calculate safe and effective doses of kanamycin for individual patients with renal insufficiency. The validity of the program was demonstrated by its ability to predict serum concentrations of kanamycin measured by microbiological assay. The principles of the program were considered potentially applicable to many other drugs (1200). Computer estimations of dosage regimens for digitalis, kanamycin, gentamicin, and lidocaine were discussed in a review article (1201). Several other reviews considered the application of computers to simulate pharmacokinetic models and to determine various pharmacokinetic parameters (1202–1205). The use of dosage regimen calculations as a facet of drug evaluation that can be implemented by the pharmacist was exemplified by tetracycline and penicillin antibiotic dosage regimens (1206).

Additional references on biopharmaceutics are listed in Table XXXV.

Effects of Physicochemical Properties—Various physicochemical parameters including solubility, surface tension, partition coefficient, vapor pressure, activity parachor, R_f values, molecular orbital calculations, and Hammett and Taft constants were correlated with the biological activity of a number of sulfonamides (1241). Rational physicochemical approaches in drug design to modulate biological action were discussed for various types of drugs (1242, 1243). A comprehensive review by Hansch and Dunn (1244) dealt with the linear relationships between lipophilic character and biological activity of drugs, a linear free energy model for structure–activity relationships, and hydrophobically sensitive and insensitive free energy relationships (1244). Determination of hydrophobicity constants and their application to structure–activity correlations of systems such as penicillin serum binding, 2-haloalkylamine adrenergic blocking activity, and *m*-nitroaniline sweeteners were reviewed. Tables of hydrophobic, electronic, and steric constants for a number of biologically active compounds were presented (1245). An interactive searching program of a structure and biological activity file, coupled with a program that scans a file of herbicidal activity of compounds, was presented. These programs were considered useful in providing background knowledge for further testing and synthesis of active drugs (1246). Utilization of operational schemes for the stepwise approach in the design of a most potent drug analog was suggested. These schemes were based on the considerations of hydrophobic, electronic, and steric effects by a particular substituent upon biological activity of the molecule (1247).

The methylene group contribution to the thermodynamics of solutions of drug molecules was obtained

Table XXXV—Additional References on Biopharmaceutics

Reference	Topic
1207	Review describing role of biopharmaceutics in the design of drug products
1208	Review of drug administration, interaction with physiological milieu, absorption, and validity of animal and *in vitro* test models
1209	Review of physicochemical and pharmacokinetic bases for the biopharmaceutical evaluation of drug bioavailability from drug formulations
1210	Review of usefulness of biopharmaceutical concepts in formulation of drugs
1211	Review discussing requirements for drugs with sustained action based on biological considerations
1212	Use of confidence intervals in analysis of comparative bioavailability data
1213	Three-phase apparatus for *in vitro* drug absorption studies
1214	Review of membrane surface and drug actions
1215	Review describing membrane transport of molecules and ions, molecular diffusion, transport across fixed-charge membranes, active transport, *etc.*
1216	Review of bioavailability as influenced by dissolution rate, and enteral absorption as a function of physicochemical properties of drugs
1217	Skin dehydration and decreased emotional arousal considered as reasons for the slower and more consistent percutaneous absorption upon repeated tests
1218	General principles of percutaneous absorption and permeation of a bioflavonoid
1219	Review discussing action of local anesthetics on excitable membranes, structure-activity correlations, and penetration through mucous membranes and skin
1220	Review of structure-activity relations and molecular pharmacology of receptors
1221	Review of drug structure and kinetics of drug-receptor interactions
1222	Review of kinetics of drug action in man, and design of safe and effective dosage regimens
1223	Review of pharmacokinetics, chemical composition, and pharmacological activity of essential oils
1224	Processes involved in drug absorption, distribution, metabolism, and excretion and their relationship to onset, duration, and intensity of drug action
1225	Equation to estimate the fraction of drug remaining in the body after intravenous injection
1226	Application of salivary salicylate data to biopharmaceutical studies of salicylates
1227	Review of drug-protein interactions as they affect drug distribution, dosage schedule, and drug use in disease states
1228	Review of drug interactions in clinical medicine
1229	Review of drug interactions as they alter pharmacokinetic parameters of a drug
1230	Review describing drug interactions during intestinal absorption, protein binding, metabolism, and excretion
1231	Review of drug incompatibility due to chemical reaction, induction of degradative enzymes, interference with absorption process, *etc.*
1232	Comparative depressant activity and interaction of ethanol and pentobarbital in goldfish
1233	Review of interactions of alcohol with CNS and cardiovascular agents
1234	Carcinogenic nitrosamines formed by interaction of nitrite with drugs containing tertiary amino groups
1235	Bioaggregational aspects of erythrocytes evaluated in terms of coagulation-flocculation theory
1236	Inhibition of platelet aggregation by bisulfite-sulfite
1237	Electrokinetic properties of bacteria studied as a function of ionic strength and pH
1238	Effect of aspirin and ethanol on the gastric mucosa of the rat
1239	Surface area term in Myhill-Piper equation for antacids
1240	Adsorption of pepsin by commercially available antacids measured *in vitro* as a function of pH

from activity coefficient, Henry's constant, and partition data. The free energy of transfer of the methylene group from water to nonpolar organic solvent was estimated as -850 cal. mole^{-1}, but for polar solvents values ranged from -712 to -452 cal. mole^{-1}. Application of these thermodynamic concepts to structure-activity relations was discussed (1248). Adoption of a thermodynamic standard state for comparing drug molecules in structure-activity studies was suggested. This standard state, acting as if it were infinitely dilute where the solvent is a suitable aliphatic hydrocarbon such as cyclohexane or isooctane, could be a 1 molal, 1 molar, or 1 mole-fraction solution (1249).

The two most frequently used regression models for structure-activity analyses, the additive and the linear multiple regression models, were shown to be fundamentally interrelated. Each approximation used in reducing the additive model to its linear multiple regression counterpart provided useful insight into how these regression methods can be best applied (1250). Statistical significance of structure-activity correlations using multiple regression analysis and the potential problems in obtaining chance correlations when many variable parameters are involved were examined. The data were presented to assess the probable degree of chance correlation as a function of the number of observations and the number of variables (1251). Suitability of the calculated electron population parameters for multiple regression analysis of biological activity was determined. It was concluded that both the CNDO/2 and *ab initio* methods of Pople *et al.*, but not extended Hückel theory, may be suitable for use in the multiple regression analysis (1252).

Quantitative relationships between physical properties and antibacterial activity of erythromycin esters were evaluated by the Free-Wilson and extrathermodynamic techniques. Both analyses indicated that esterification decreases activity; this decrease increases with increasing chain length of the ester. The extrathermodynamic equations suggested that the partition coefficient is an important determinant of activity (1253). Antibacterial activity of rifamycins was shown to correlate with the chromatographic substituent constant R_m (1254). The structure-activity relations of penicillins were discussed in several reviews (1255–1257). Analgesic activity of *p*-substituted acetanilides showed better correlation with the chromatographic substituent constant R_m than with the Hansch hydrophobic substituent constant π (1258). The structure-activity relationships in the anesthetic action of aliphatic ethers were found to be parabolic functions of their octanol-water partition coefficients. An optimum lipophilic character (log P_0) of about 2 was determined for general anesthetics, which is comparable to that obtained for barbiturates, ureas, alcohols, *etc.* (1259).

Correlations between steric, electronic, and hydrophobic parameters and biological activity were estab-

lished for 2-phenylquinoline-4-carbinol antimalarials (1260), 1,3-dioxolane cholinergics (1261), tricyclic neuroleptics and antidepressants (1262), anti-inflammatory 3-(5-aryl-2-tetrazolyl)alkanoic acid derivatives (1263), hemolytic activity of polyene antibiotics (1264), decahydroisoquinolines possessing antiarrhythmic activity (1265), veratrum alkaloids (1266), and a series of 2*H*-1,2,4-benzothiadiazine 1,1-dioxide antihypertensive compounds (1267, 1268). The steric and electronic parameters of styrylpyridine analogs were correlated with their choline acetyltransferase inhibitory activity in an effort to elucidate the nature of interactions of this type of inhibitor with the enzyme. Hydrophobic and electron-donor contributions by the aryl moiety and electron-acceptor characteristics of the pyridinium moiety were believed to be involved in the inhibitor–enzyme binding (1269). A similar approach to structure–activity correlation was applied to study interactions of acetylcholinesterase with substituted phenylammonium iodide inhibitors (1270). The parts of the inhibitor molecule that contribute to the hydrophobic bonding with the enzyme might only be the parts that are in contact with the enzyme. Such a directional nature of hydrophobic bonding was demonstrated in the case of phenylethanolamine *N*-methyltransferase inhibitors (1271). The lipophilicity of some hexamethonium analogs was compared with their ganglionic blocking activity. The compounds more lipophilic than hexamethonium were less active than hexamethonium, but the lipophilic character of a highly active analog was comparable to that of hexamethonium (1272, 1273).

Theoretical prediction of the influence of complex formation on the transport rate of a drug and computation methods were described by Vaidhyanathan (1274, 1275). It was shown that complexation of a drug with a substance of lower diffusion coefficient leads to enhancement of the transport rate of the drug; complexation with substances having similar diffusion coefficients, however, results in reduction of the transport rate (1274). Fluxes of drugs across membranes affected by the presence of a complexing agent in the membrane were represented by a generalized form of Fick's law, which accounts for the existence of coupling between fluxes of different species (1275). A series of publications by Hayton and coworkers (1276–1281) dealt with the subject of drug complexation and its effect on drug absorption. The effects of certain *N,N*-dialkyl propionamides on the permeability of the rat small intestine and of a synthetic lipoid barrier to prednisone and prednisolone were investigated. Enhancement in the intestinal absorption of these drugs by *N,N*-dibutyl- and *N,N*-dipropylpropionamide appeared to be due to the formation of a steroid–amide complex in the intestinal barriers. However, the intestinal absorption of several nonsteroid drugs which complex with the amides was not significantly affected by these amides. This indicated that the absorption-enhancing effect of the amides was relatively specific to a drug. Some structural features of the steroid molecule required for the enhancement of drug absorption by its complexation with an amide were considered (1276–1281). The transfer process of various acidic drugs from water into chloroform containing phospholipids was examined using a nonemulsifying system. The ionized forms of the drugs with little lipid solubility showed a marked increase in transfer to the chloroform phase containing lecithin at the physiological pH of the small intestines. These results indicated the possible role of phospholipids in the intestinal absorption of ionized acidic drugs (1282).

Relationships between surface activity and biological activity of drugs were reviewed for local anesthetics, sedatives and hypnotics, antibacterial agents, hormones, fat-soluble vitamins, and miscellaneous drugs (1283). Iso-branched fatty acids, with fungistatic and bacteriostatic properties, were found to enhance the effect of conventional antimicrobial agents acting inside the cell membrane. A molecular mechanism for this effect was proposed on the basis of surface film studies (1284). Molecular interactions between quaternary ammonium surfactant bactericides and bacterial cell wall constituents were studied by means of surface film balance and conductometric methods. The results suggested that in Gram-positive organisms, the bactericide first becomes associated with the protein in the cell wall; subsequent penetration leads to disruption of the cell membrane. In Gram-negative organisms, the phospholipid present in the cell wall affords the organism a degree of protection from the bactericide (1285, 1286).

Additional studies on the effects of physicochemical properties are listed in Table XXXVI.

Effects of Formulation—Two crystal forms of the drug sulfameter were orally administered to man. The absorption rate was about 1.4 times greater with the more energetic metastable crystal form than with the stable crystal form; the results were discussed in relation to the free energy differences between the two crystal forms and their *in vitro* dissolution rates (1316). The rate and extent of reserpine absorption in rats were significantly enhanced upon oral administration of reserpine–polyvinylpyrrolidone coprecipitates. The fraction of the oral dose absorbed was 2–3 times greater with the coprecipitate than with either the pure drug or physical mixtures of drug with polyvinylpyrrolidone. The *in vivo* absorption data were consistent with the *in vitro* dissolution characteristics of the tested drug forms (1317, 1318). Crystalline and amorphous preparation of asparaginase were found comparable with regard to toxicity and capacity to induce remission of acute leukemia in children (1319).

The absorption of orally administered riboflavin-5′-phosphate by healthy male subjects was increased significantly when it was given in 50 ml. of 2% sodium alginate solution rather than in the aqueous vehicle without sodium alginate. Retention of the vitamin at specialized absorption sites for prolonged time periods because of the slow movement of the highly viscous sodium alginate solution was proposed as the rationale for the absorption data (1320). Oral administration of sodium *p*-aminosalicylate with methylcellulose and gum arabic to rats produced higher but delayed absorption, probably due to a viscosity effect; administration with surface-active agents in concentrations below the CMC considerably increased the drug absorption (1321).

Table XXXVI—Additional References on Effects of Physicochemical Properties

Reference	Topic
1287	Review of the Free-Wilson method and Hansch multiple regression analysis method for structure-activity correlations
1288	Review of quantitative structure-activity correlations by using Hammett and Taft constants and partition coefficient parameters
1289	Review of various factors that may affect the interpretation of drug structure-activity relations
1290	Role of partitioning phenomena in drug absorption distribution; review of response and elimination
1291	Review of physicochemical and biological factors influencing concentration of drugs at body sites
1292	Structure-activity relationship in the taste effect of ribonucleotide derivatives
1293	Review of molecular orbital approach to quantitative drug design illustrated by benzothiadiazines
1294	Review of application of molecular orbital theory to drug-receptor mapping
1295	Influence of electron-donating properties on the psychotropic activity of phenothiazine derivatives
1296	Conformational and structural relationships among antipeptic ulcer compounds
1297	Review of physicochemical properties of dextran solutions and their pharmacological effects
1298	Comparative physicochemical studies of plasma substitutes
1299	Review of modulation of drug pharmacokinetics by alterations in biofunctional moieties
1300	Review of relation between partition coefficients and drug action
1301	pK values and their significance in enteral resorption
1302	Physicochemical properties of polyene macrolide esters and salts of amphotericin and their biological activity
1303	Review of structure-activity relationships for digitalis glycosides
1304	Review of structure-activity relationships between acetylcholine and quaternary ammonium neuromuscular blocking agents
1305	Review of correlation between lipid solubility and biological action of homologous local anesthetics
1306	Structure-activity correlation for substrates of phenylethanolamine *N*-methyltransferase
1307	Microbiological determination of drug partitioning and protein binding in complex coacervate model systems
1308	Relationship between antibacterial activities in rabbit serum and protein binding of mitomycin derivatives
1309	Influence of protein binding of chlorpromazine upon pharmacokinetic parameters in man, dog, and rats
1310	Inhibition of folate synthesis by sulfonamides correlated with their antibacterial activity and physicochemical parameters
1311	Relation between biological activity and the degree of resolution of optical isomers of phenylcyclohexylglycolloylcholine and benzhexol
1312	Association constants of various amphetamine molecular complexes correlated linearly with the threshold hallucinogenic dose in humans
1313	Influence of organic phase composition on distribution coefficient of weak polar bases
1314	Review of structure-activity relationships between drugs and bioreceptors in terms of three-dimensionally defined molecular entities
1315	Correlations between kinetics of drug-receptor interaction and chemical structure of cholinomimetic agents

Partition coefficients of ionized and unionized salicylic acid molecules between water and the micelles of several nonionic surfactants were determined. The results were discussed in terms of their significance to the process of drug absorption from surfactant solutions (1322). The influence of macromolecular nonionic agents such as polyethylene glycol, methylcellulose, and polyvinyl alcohol on the enzymatic activity of pepsin, amylase, invertase, and lipase was investigated. Most of the high viscosity polymers tested decreased to a varying degree the activity of these enzymes (1323–1325). Samples of dicumarol (bishydroxycoumarin), equilibrated with various tablet excipients, were administered to dogs to determine the excipient effects on the drug absorption. Administration of the drug with talc, colloidal magnesium aluminum silicate (Veegum), aluminum hydroxide, or starch resulted in significantly lower plasma levels of the drug; but with magnesium oxide and hydroxide, plasma levels of the drug were higher than for the drug administered alone. In further work, *in vitro* dissolution characteristics of three commercial brands of dicumarol (bishydroxycoumarin) tablets were shown to correlate positively with the *in vivo* plasma levels of the drug. As a second phase of the study, application of diffuse reflectance spectroscopy in evaluating physical stability of simple emulsion bases and chemical stability of various drugs within an emulsion was demonstrated (1326).

Blood salicylate levels after administration of aspirin preparations of varying particle sizes to rabbits indicated that the absorption rate was inversely proportional to the particle size; however, the absorption rates of aspirin particles coated with 10% precirol were approximately the same regardless of particle size (1327). Four buffered aspirin tablets were tested for their *in vitro* dissolution rate, buffer capacity, absorption rate, and induced GI bleeding in normal human subjects. An inverse rank-order correlation was found between buffer capacity and GI bleeding (1328). In a comparative study with four commercial enteric-coated aspirin tablets, disintegration times in pH 6 buffer solution correlated with the drug absorption rates in humans (1329). Significant differences were observed in the absorption characteristics of three commercial tetracycline preparations. These differences were observed after both single-dose and multiple-dose administration (1330). The *in vitro* dissolution rates of tablet and capsule dosage forms of diazoxide in 0.1 *N* hydrochloric acid and of griseofulvin in simulated intestinal fluid were shown to correlate linearly with the blood levels of the respective drugs (1331). Tablet, capsule, and suspension formulations containing trimethoprim and sulfamethoxazole were considered bioequivalent in humans on the basis of blood level data (1332).

Timed-release tablet formulations of sulfamethizole consisting of a lipase–lipid system as the release-controlling vehicle were studied for their *in vitro* release rates and *in vivo* absorption patterns in dogs. Uniform blood levels over 12 hr. were observed following oral administration of the tablets. Lipolytic digestion of the lipid was considered as the primary factor in the timed-

release rates of the drug (1333). Three slow-release preparations of isoniazid were studied in man for their potential use as once-a-week dosage forms in the treatment of tuberculosis; a matrix-type formulation was considered therapeutically effective (1334). The cancer chemotherapeutic agents sodium methotrexate, vincristine sulfate, and cytosine arabinoside provided timed-release activity in mice when administered in multiple-emulsion injectable formulations (1335). A timed-release multiple emulsion was used to extend the radioprotective action of cysteamine in mice (1336). Determination of blood phenobarbital levels in minipigs or dogs, during long-term administration of the drug in conventional or three timed-release dosage forms, failed to show any advantage with the timed-release formulations (1337).

Pharmaceutical aspects of corticosteroids in dermatological preparations, such as uptake of steroids from ointments by the skin, physical and chemical modification of the steroids during manufacture, and modification of the carrier, were reviewed (1338). Selection of a particular base vehicle for topical formulation of each individual drug to obtain optimum therapeutic activity was demonstrated by comparing activities of fluocinonide and fluocinolone acetonide in the same vehicle with intrinsic activities of the drugs. Fluocinolone acetonide was readily released from the base and exhibited significant clinical effectiveness; however, fluocinonide activity was considerably reduced because of poor drug release from the base (1339). Ointment preparations of betamethasone 17-benzoate in white soft paraffin and propylene glycol or in white paraffin and isopropyl myristate showed higher vasoconstrictor activity in humans than five other ointments tested, including water-miscible ointments based on polyethylene glycols (macrogols) (1340).

The rate of water desorption of untreated and surfactant-treated depilated rabbit skin was determined to supplement previous data of surfactant-induced changes in biological membranes. The water desorption rate was always greater with the surfactant-treated than with the control skin. The results confirmed earlier findings that the tested nonionic surfactants affect membrane structure, thereby increasing skin permeability (1341). Various sunscreening, deodorant, antiperspirant, and insect repellent preparations were studied to determine the effect of formulation variables on the skin retention of the medicament and efficacy of the formulation. The retention of the drug on human skin was correlated with the solubility and partition coefficient of the drug (1342). The delayed rate of onset of erythema on the human skin induced by methyl nicotinate in aqueous glycerol solutions appeared to be related to the decreased partition coefficient and diffusivity of the drug in these solutions (1343). A correlation was established between the diffusion of ditetracycline from ointment bases of various chemical nature through agar and its permeation through rabbit conjunctiva (1344). Relative rates of percutaneous absorption from hydrophilic and lipophilic ointment bases were evaluated for 4-bromophenyl isothiocyanate-^{35}S (1345) and salts of 8-hydroxyquinoline and procaine (1346). The anti-inflammatory effect of ichthammol (Ichthyol) ointments was shown to correlate with the dielectric constant of the preparation (1347).

Properties of ophthalmic formulations, such as pH, isotonicity, hydrophilic and lipophilic bases, and medicament, that affect absorption through the cornea were discussed by Silverman (1348). The adjuvant effect on intramuscular drug absorption was investigated by *in vivo* absorption studies in rats and *in vitro* diffusion model experiments. The absorption rate correlated with the viscosity of the injectable preparation for adjuvants having relatively small molecular size such as propylene glycol, glycerin, and polyethylene glycol 400. From *in vitro* diffusion studies, it was concluded that the contribution of the diffusion process through the pores of the capillary wall was dominant compared with diffusion through muscle fiber space (1349). The degree of tissue lesion in rat quadriceps femoris muscles following intramuscular injections of aqueous formaldehyde was studied as a function of duration, concentration, solvent composition, and volume of the injected solution. The extent of tissue lesion was proportional to the concentration and postinjection time, and it was twofold larger with ethanol than with glycerol formaldehyde (1350, 1351). A method for clinically evaluating pain of injection for parenteral preparations was described (1352).

Additional references on the effects of formulation are listed in Table XXXVII.

Absorption Control and Alteration—This section of biopharmaceutics is comprised of studies related to control and alteration of drug absorption by coadministration of drugs or a drug with other chemical agents, disease, blood flow, food, route of administration, and age.

Parallel *in vitro* and *in vivo* determinations of adsorption characteristics of activated charcoal were carried out with drugs having different pKa's: aspirin, salicylamide, and phenylpropanolamine. Adsorption and desorption characteristics of these drugs, evaluated by *in vitro* tests, were predictive of the effect of dose and mode of charcoal administration on its antidotal effectiveness in humans (1387, 1388). Prompt administration of a sufficient quantity of activated charcoal had a significant inhibitory effect on the absorption of aspirin from solution, conventional tablets, enteric-coated tablets, and timed-release tablets. Aspirin absorption can be reduced even if activated charcoal is administered 3 hours after aspirin ingestion, provided that the drug is still in the GI tract at that time (1389). Drug adsorption efficacy of commercial activated charcoal tablets and activated charcoal powder was compared by *in vitro* tests and in man, using phenylpropanolamine as the test drug. The rate and extent of drug adsorption by charcoal tablets *in vitro* were much lower than by the powder. Equal doses of charcoal tablets and powder reduced phenylpropanolamine absorption in man by 48 and 73%, respectively (1390). Similar inhibitory effects of activated charcoal were also observed for the absorption of sulfamethazine (sulfadimidine) and sulfaguanidine (1391). The absorption of diazepam in man from a suspension formulation containing colloidal magnesium aluminum silicate (Veegum) was slower than from a solution preparation

Table XXXVII—Additional References on Effects of Formulation

Reference	Topic
1353	Review of factors influencing physiological availability of drugs from tablets
1354	Comparative bioavailability study for three commercial brands of oxytetracycline hydrochloride
1355	Variation in bioavailability of digoxin tablets attributed to tablet disintegration
1356	Review emphasizing importance of chemical and physical formulation factors in drug absorption process
1357	Review discussing influence of formulation on drug action
1358	Comparison of *in vitro* dissolution rates of phenobarbital tablets in relation to possible effects on drug absorption
1359	Comparison of capsule, tablet, and intravenous infusion of quinine in an open, multidose crossover study; toxicity effects
1360	Effects of antacids on oral absorption of sulfadiazine and quinidine
1361	Review discussing effect of other drugs and surfactants on the activity of local anesthetics
1362	Use of hydantoic acids, hydantoic acid esters, and *N*-acyl phthalimides as water-soluble prodrugs
1363	Increased resorption of anesthetics and antibiotics by addition of hyaluronidase in suppositories and ointments; effect of trypsin and chymotrypsin on the resorption of penicillin and tetracycline
1364	Lack of correlation between physiological availability of commercial triple sulfa preparations and *in vitro* dissolution rates
1365	Digestive action of enzyme substitutes shown to be dependent on the composition, method of preparation, and proper enzyme release rates
1366	Variation in bioavailability among seven commercial brands of phenylbutazone tablets sold in Finland
1367	Plasma concentrations of proxyphylline following repeated administration of timed-release tablets similar to conventional tablets after 4th day of administration
1368	Selective review of the methods and principles used to assess effects of excipients on drug absorption
1369	Effectiveness of rifamycin derivatives as inhibitors of polymerase activity reduced in presence of nonionic surfactants
1370	Combined effects of surfactants with germicidal compounds; activity of butylparaben reduced in presence of nonionic surfactants
1371	Comparison of four vehicles for intraperitoneal administration of Δ^1-tetrahydrocannabinol
1372	Clindamycin palmitate flavored granules with rapid absorption and excretion and good tolerance to multiple dosing in children
1373	Clindamycin palmitate flavored granules equally absorbed before or after meals
1374	Delayed onset of action obtained upon intraperitoneal or subcutaneous administration of barbituric acids in emulsion formulation
1375	Anti-inflammatory action of phenylbutazone in a polyethylene glycol ointment base enhanced by the presence of a chymotrypsin complex
1376	Evaluation of antiseptic effect of five topical anesthetic ointments
1377	Percutaneous absorption of estradiol benzoate from polyethylene glycol vehicles
1378	Comparative evaluation of percutaneous absorption of drug through rabbit, dog, and guinea pig skin to develop an animal model for dermatological research
1379	Effect of vaselinum flavum and different batches of cera liquida ointment bases on epidermal width and mitotic activity
1380	Rate of absorption of salicylic acid through animal skin faster from a nonaqueous ointment base than from a hydrophilic base
1381	Sodium lauryl sulfate enhancement of the rate of penetration of glycol salicylate administered cutaneously and rectally
1382	Effects of excipients and surfactants on rectal absorption of erythromycin
1383	Formulation factors influencing rectal absorption of *N*-pyrrolidinomethyltetracycline guaiacolsulfonate
1384	Polysorbate 80 in concentrations of less than 10% considered suitable for intravaginal formulations
1385	Liposomes as carriers of enzymes or drugs—an approach to the treatment of storage diseases
1386	Review of factors influencing release and absorption of drugs from ointment bases

without it. This was attributed to the desorption of diazepam from the emulsifier as a rate-limiting factor in the drug absorption process (1392).

Cholestyramine, an anion-exchange resin with hypocholesterolemic activity, was shown to interact strongly and rapidly with the antibiotic sodium fusidate. As suggested by the *in vitro* results, concurrent oral administration of the resin and sodium fusidate to rats yielded statistically significant reductions in serum antibiotic levels at all experimental time intervals. *In vitro* adsorption studies also demonstrated that physiological bile salt and fatty acid anions effectively compete with fusidate anions for the available binding positions on the resin (1393, 1394). Inhibition of iron and vitamin B_{12} absorption by cholestyramine was considered the reason for the observed iron and vitamin B_{12} deficiency in rats following prolonged administration of the resin (1395). Various factors influencing the absorption of vitamin B_{12} (*e.g.*, food, charcoal, and pentagastrin) were studied in healthy subjects and in patients with pernicious anemia. The drug absorption in patients was decreased by simultaneous administration of charcoal (1396). The oral absorption of ^{57}Co-labeled vitamin B_{12} at low doses in cats was enhanced by coadministration of dog or human pancreatic juice (1397). Effects of sugars, polyalcohols, and organic acids on hydrolytic polymerization of iron were examined. The results suggested that these compounds enhance the absorption of iron across the intestine by formation of low molecular polymers of iron (1398).

The effect of tetracyclines on the intestinal absorption of sulfonamides was investigated by the recirculation and loop methods in the rat. At pH 6 and 8, demeclocycline (demethylchlortetracycline) and methacycline (methyleneoxytetracycline) enhanced the absorption of sulfaguanidine, while tetracycline enhanced the sulfa drug absorption only at pH 8 (1399). In a subsequent study, the amount of intravenously administered sulfa drug exsorbed into the intestine was examined with the intestine either perfused with tetracycline solution or isotonic buffer. The effect of tetracycline on the absorption and exsorption of sulfa drugs was attributed to changes in the small intestinal tissue by tetracycline (1400). Specific inhibition of cholesterol absorption in rats and mice was shown to occur with sulfaguanidine but not with other structural analogs of the sulfa drug (1401). The influence of polybasic antibiotics and sulfaguanidine on the absorption and excretion of

cholesterol and bile salts was discussed in a review article (1402). Heparinic acid and its acid salts were readily absorbed from the intestine to provide systemic anticoagulant activity in rabbits, monkeys, and dogs. Increased absorbability, however, was accompanied by a decrease in stability. Weak nitrogenous bases such as nicotinamide were complexed with heparinic acid to give compounds with high absorbability coupled with good stability (1403). The absorption of streptomycin from uterine and salpingeal mucosa was significantly greater when the drug was applied with hyaluronidase; the absorption was further enhanced when galvanic current was introduced during intrauterine electrophoresis (1404).

Oral administration of the anticholinergic drug propantheline bromide to healthy adult males 30–60 min. before an oral dose of riboflavin phosphate delayed the absorption of the vitamin but caused a pronounced increase in total amount absorbed. This was attributed to delayed gastric emptying and slowed transit of riboflavin solution through the small intestinal lumen due to the anticholinergic effect of propantheline (1405). However, oral administration of aminopyrine with barbital produced significantly higher initial plasma levels of aminopyrine, which were attributed to the increased rate of gastric emptying induced by barbital (1406). Magnesium hydroxide and aluminum hydroxide given by gastric intubation to the rat prior to, or simultaneously with, sodium pentobarbital decreased GI absorption of pentobarbital and delayed the onset of sleep. Magnesium hydroxide, by raising the gastric pH, allowed the drug to remain in the ionized unabsorbable form while aluminum hydroxide acted by delaying gastric emptying time. Although these antacids decreased the absorption rate of pentobarbital, the total amount absorbed remained unaltered (1407). Enhanced absorption of pseudoephedrine by concurrent administration of aluminum hydroxide gel was ascribed to the increase in GI pH caused by the antacid (1408). Intestinal absorption of tritiated folic acid in human subjects with a triple lumen tube positioned in the proximal jejunum was decreased by about 44% after perfusion with diphenylhydantoin. This inhibition of folic acid absorption was considered as a likely reason for the folate deficiency that occurs with diphenylhydantoin therapy (1409).

Rapid penetration of gentamicin in the aqueous humor of rabbit eyes with corneal ulcers occurred when the antibiotic was administered by subconjunctival injection, topical drops, or continuous lavage. Concomitant serum levels of gentamicin were lowest when topical drops were used (1410). In a review paper, calculation of multiple-dosage schedules for maintenance of desired drug levels in anuric patients and elimination rate constants of several drugs in such patients were presented (1411). Acetaminophen (paracetamol), taken orally after overnight fasting, was absorbed up to five times faster but to the same extent as when it was taken after a high carbohydrate breakfast. Subjects taking the drug immediately before sleep excreted up to 36% less than after taking it in the morning (1412). The presence of food in the intestine decreased the *in vivo* uptake rate of anisotropine methylbromide in the rat but had no effect on the total uptake. The sum of drug bound to intestinal tissue and that taken into the circulation was 48% of the dose administered (1413). Absorption of ampicillin and nalidixic acid by infants and children with acute shigellosis was determined. Five of the 16 patients receiving nalidixic acid had a pronounced delay in absorption, while 10 of 21 ampicillin-treated patients showed depressed plasma levels and prolonged half-lives (1414). A mathematical model was described to explain the apparent difference in the rate of increase of alveolar halothane concentration between children and adults. Concentration of the anesthetic used, cardiac output, and metabolic rate were considered as reasons for the observed difference (1415). Since intestinal absorption of tritiated 25-hydroxycholecalciferol was about the same in both normal children and those with osteopathies, it was concluded that the resistance of osteopathies to the drug therapy is not because of malabsorption of the drug (1416).

Oral doses required for a drug are sometimes larger than are needed by the parenteral route of administration. This might be the case when a large fraction of the oral dose is eliminated on first passage through the liver. An equation derived based on these considerations provided an estimation of the availability of a completely absorbed, orally administered drug. The importance of clearance concepts in bioavailability studies, drug design, and enzyme induction studies was discussed (1417). The antagonism of isoproterenol-induced tachycardia by orally and intravenously administered propranolol was measured in five subjects and related to the plasma propranolol concentration. The degree of β-blockade at a given plasma drug concentration observed 2 hr. after oral administration of a single dose of propranolol was greater than with intravenous administration. This was explained by the formation of an active metabolite, 4-hydroxypropranolol, only after a single oral dose; this metabolite has a shorter half-life than the parent drug (1418).

Polyinosinic acid–polycytidylic acid was given to rabbits by intravenous, intraocular, and topical ocular routes. A pyrogenic response was achieved by all three routes. The minimum pyrogenic doses were 0.1, 1.0, and 1000 mcg./kg. for intravenous, intraocular, and topical ocular administrations, respectively. Ocular responses of the drug paralleled the pyrogenic responses (1419, 1420). Streptomycin concentration in lung tissue and bronchii of tuberculosis patients was three to four times higher for 12 hr. after intratracheal–bronchial administration than after intramuscular or intravenous injection. Clinical effectiveness of the drug administered by the intratracheal route was increased by simultaneous general antibacterial therapy (1421). Inhalation by asthma patients of beclomethasone dipropionate from a pressurized aerosol exerted a significant topical action on the airways, with the expected clinical response (1422). A more lasting and effective clearing of airways in asthmatic patients was obtained by administering rimiterol in aerosol form in frequent small inhalations rather than in a single larger dose (1423).

Additional references on absorption control and alteration are listed in Table XXXVIII.

Table XXXVIII—Additional References on Absorption Control and Alteration

Reference	Topic
1424	Administration of two or more related drugs to study the effect of molecular modification and formulation on drug absorption, metabolism, and excretion
1425	Influence of vitamin D on intestinal calcium transport in normal rats
1426	Effect of phenobarbital on intestinal calcium transport in rats
1427	Intestinal absorption of the radiographic contrast agent iopanoic acid accelerated with increase in GI pH
1428	Ocular absorption of catecholamines altered by ionic composition of the vehicle influencing corneal epithelium permeability
1429	Effect of chemical form of orally administered zinc on absorption and metabolism in cattle
1430	Aluminum complex of dextran sulfate better absorbed from small intestine than sodium salt of the polymer
1431	Drug therapy dependence upon the route of administration, plasma concentration, rate of elimination, and other body conditions
1432	Blood levels of morphocycline and neomycin lowered in dogs by concurrent intravenous administration of heparin
1433	Dioctyl sodium sulfosuccinate acceleration of peritoneal dialysis of urea and phosphate but not of creatinine in rabbits
1434	Effects of ε-aminocaproic acid on radiation-induced increase in capillary permeability of the skin
1435	Effects of nonionic surfactants that modify experimental tuberculosis on lipase activity of macrophages; correlation with surfactant chain length
1436	Salicylic acid absorption and excretion rates after oral administration of salicylic acid–choleic acid inclusion compound in suspension form
1437	Longer duration of drug action for catecholamines covalently bound to porous glass particles
1438	Changes in aspirin potency in the presence of protein-bound dye
1439	Review of analgesic synergism of aspirin and binding sites of salicylates on plasma proteins
1440	Effects of riboflavin on boric acid toxicity; riboflavin depletion induced by borate
1441	Comparison of the chemical stability and oral absorption in rabbits of ascorbic acid complexes with organic bases
1442	Conjugates of nitrogen mustards with proteins, polypeptidyl proteins, and polypeptides as cytotoxic agents with higher therapeutic indexes
1443	Nitrogen mustard–serum protein complexes with higher antitumor activity than the drug alone
1444	Slower absorption of benzoic acid and hydroxybenzoic acids through *in situ* rat gut from solutions containing polyvinylpyrrolidone
1445	Review of local and systemic factors controlling human sebaceous activity
1446	Normal absorption of vitamin B_{12} in chronic pancreatitis patients in nonfasting state
1447	Enteral absorption of drugs in rats of different ages
1448	Role of modes and sites of administration of cortisol and cortisone upon drug metabolism
1449	Effects of high altitude exposure on the rate of ingesta flow in the GI tract of the rat
1450	GI calcium absorption in nephrolithiasis
1451	Inhibition of glucose absorption by prostaglandins E_1, E_2, and $F_{2\alpha}$
1452	Effect of dicumarol (bishydroxycoumarin) on intestinal absorption of D-mannose and D-xylose
1453	Analysis of the inhibitory effect of biguanides on glucose absorption
1454	Effects of tolbutamide and glyburide on intestinal glucose absorption
1455	Site of intestinal absorption of sodium taurocholate and its consequence on drug absorption in the rat
1456	Chloramphenicol plasma levels in the dog after multiple oral and intramuscular administration
1457	Chloramphenicol plasma levels in the dog after oral, subcutaneous, and intramuscular administration
1458	Comparison of intradermal and subcutaneous routes of cholera vaccine administration
1459	Significantly slower absorption of ephedrine analogs after percutaneous than after oral administration
1460	Review of relations between the mode of administration and the pharmacodynamics of a drug and its plasma levels
1461	Decreased plasma levels of dicumarol (bishydroxycoumarin) after hypnotic doses of phenobarbital, glutethimide, or methaqualone administered orally to rats

Absorption Mechanisms—Mucosal-to-serosal flux of a number of solutes across the rat everted small intestine was determined as a function of time. The transfer rates of certain solutes progressively increased during the experiment, which was attributed partially to a loss of functional integrity of the intestine with respect to passive transfer (1462). Histological changes in the rat small intestine induced by edetate (EDTA), tetracycline, and sodium lauryl sulfate were examined using light and scanning electron microscopes. The observations provided further insight into the possible mechanism for the facilitative absorption of poorly absorbed drugs by these agents (1463). Concurrent absorption of water from the *in situ* rat small intestine during drug absorption experiments indicated that approximately 4 ml. of water was lost from the intestine during 60 min. The importance of considering the rate of water absorption to estimate accurately a drug absorption rate constant was emphasized (1464). The influence of net water transfer on drug absorption in an *in situ* rat intestinal preparation was studied using hypotonic, hypertonic, and isotonic intestinal lumenal solutions. The results indicated that the intestinal water loss or gain which occurred with the different tonicity solutions did alter the apparent rate constant for sulfaethidole absorption. When the apparent rate constants were corrected for the liquid volume and relative available surface area, permeability constants of sulfaethidole were comparable for the isotonic and hypotonic solutions, but a reduced permeability constant was obtained with the hypertonic solution (1465). Intestinal absorption of drug was positively correlated with the blood flow by the determination of absorption rates from perfused rat jejunal loops at different levels of blood flow. A mathematical model for intestinal drug absorption was discussed (1466).

The principal mechanisms of drug transport through the skin, the respiratory tract, and the GI tract were discussed. Two kinds of absorption regions were described: (*a*) the lipid protein matrix for the penetration of lipophilic substances, and (*b*) intercellular pores for hydrophilic substances (1467). Permeation of ions through *Necturus* gallbladder epithelium was shown to occur mainly through the intercellular junctions, thus bypassing the epithelial cells (1468). The mechanism by which surfactants affect drug absorption was studied by

measuring the rate of permeation of chloramphenicol through model membranes in the presence of surfactants. The rate was related to the extent of drug binding to the bovine serum albumin transport barrier and was controlled by competitive binding of the surfactant molecules (1469). The diffusion of hydrocortisone across a cellulose acetate membrane and the effects of *n*-alkyl polyethylene surfactants on the drug transport were explained by the thermodynamics of the test system (1470). A protein of about 12,000 molecular weight, which binds long-chain fatty acids and certain other lipids, was identified in cytosol of intestinal mucosa, liver, myocardium, and other tissues. The presence of this protein was regarded as a possible reason for the previously observed differences in intestinal absorption among fatty acids (1471).

The absorption of quinine and chlorpheniramine through the rat rectum, small intestine, and stomach was enhanced in the presence of anionic agents. Although enhancement of absorption was related to partition behavior, organic solvent, and surface activity of ion-pair complexes, these properties alone failed to provide a complete explanation for the observed effect (1472). The intestinal absorption of two poorly absorbed quaternary ammonium drugs, hexamethonium chloride and pralidoxime chloride, in the presence of various organic and inorganic anions was investigated using a modified *in situ* gut technique. Enhanced absorption of these drugs by cholate and phoscholate ions was attributed to the effect of these anions on the structural integrity of the membrane tissue. A kinetic model was suggested for the possible mechanism of absorption of quaternary ammonium drugs (1473). Kakemi and coworkers (1474–1476) investigated the intestinal absorption of sulfapyridine, salicylamide, acetanilide, and methyl orange from oil solutions and oil-in-water emulsions in rats, using *in situ* recirculation and loop techniques. In the absorption of drugs having partition coefficients greater than one, the amount of drug in the aqueous phase of the emulsion was the critical factor in the absorption process. Two possible mechanisms for methyl orange transport were proposed: passive transport and an active-like process involving enzymatic reduction of methyl orange on the mucosal side of the membrane (1474–1476). Major pathways involved in the GI absorption of sodium nitrite and its concentration in the mouse stomach 10 min. after oral administration were determined. The major pathway for the nitrite absorption was directly from the stomach into the bloodstream (1477).

In a comparative study, percutaneous absorption of haloprogin, *N*-acetylcysteine, cortisone, testosterone, caffeine, and butter yellow was shown to occur at a decreasing rate in the order: rabbit, rat, miniature swine, and man, with the swine having the closest permeability characteristics to human skin (1478). Absorption profiles of intramuscularly administered cationic drugs, protonated at physiological pH, were studied using the rat thigh muscle clearance method and *in vitro* uptake experiments. The storage or affinity of these drugs for the muscle tissue was proposed as one factor responsible for the low absorptive nature of cationic drugs (1479).

Subcutaneous absorption of a series of local anesthetics, chemically related to lidocaine, was investigated in anesthetized rats using the system of Ballard and Menczel. The results concurred with the proposed mechanism for subcutaneous absorption involving two processes: (*a*) spreading into surrounding connective tissue, and (*b*) absorption through capillaries (1480, 1481). Absorption of saccharides and urea from the rat lung appeared to be mainly by the process of diffusion (1482). A subsequent study dealt with the absorption of various drugs (*e.g.*, antipyrine, pentobarbital, and salicylic acid) from the rat lung. Comparison of absorption rate constants with chloroform–water partition coefficients and aqueous diffusion coefficients of the drugs suggested that these drugs are absorbed by diffusion across a lipoid–pore membrane. Absorption of drugs was significantly faster from the lungs than from the small intestine (1483). Solubilization as a mechanism of gas transport in biological systems by aggregation through associated micelle formation was investigated. Halothane, ether (ethyl), trichloroethylene, and nitrous oxide were used with surfactant systems of polysorbate 80, dioctyl sodium sulfosuccinate, and bovine albumin; a modified tonometer was used as an absorption chamber (1484).

Additional references on absorption mechanisms are listed in Table XXXIX.

Drug Absorption—Oral absorption characteristics of a systemic anti-inflammatory agent, naproxen, was studied in beagle dogs. Complete absorption of the drug was observed, with the absorption occurring at a significantly faster rate from the sodium salt and calcium salt of the drug than from the unmicronized form of the drug. No significant differences were noticed in the rate and extent of drug absorption in man between tablet and capsule formulations of this drug (1510). The absorption, distribution, metabolism, and excretion of naproxen were studied in rats, dogs, monkeys, and human subjects after either oral or intravenous administration. The drug administered orally was rapidly absorbed in all species; all except the dog excreted naproxen plus its metabolites predominantly in the urine (1511). When propantheline labeled with ^{14}C in its xanthene carboxylic moiety was administered orally or intrajejunally to healthy subjects, the absorption of the intact drug after oral administration was estimated to be less than 50% (1512). Transformation of 1-β-D-arabinofuranosylcytosine to 1-β-D-arabinofuranosyluracil by the intestinal microflora of the rat seemed to be partially responsible for the poor absorption of the orally administered drug. This was further evidenced by a twofold increase in the drug absorption by coadministration with antibiotics (1513). Salicylazosulfapyridine was also extensively metabolized in the human digestive tract, presumably by the action of the gut flora (1514).

The oral absorption of mepenzolate bromide in humans was studied by administration of the drug in solution or capsule dosage forms. In either case, an average of 14% of the total administered drug was eliminated in the urine, thus indicating substantial oral absorption of this quaternary onium-type drug (1515). Kinetics of absorption and elimination of pralidoxime

Table XXXIX—Additional References on Absorption Mechanisms

Reference	Topic
1485	Review of physiology and biochemistry of intestinal absorption; factors affecting drug absorption
1486	Review of absorption of drugs through oral mucosa
1487	Review describing active transport and mechanisms of membrane permeation including drug effects, diffusion, transfer of ions, and macromolecules
1488	Ionic movement across the gastric mucosa of man; reproducibility and effect of intravenous atropine
1489	Mediative role of sodium in intestinal calcium transport considered to involve activation of an enzyme complex
1490	Mechanism of absorption of salicylic acid and its isomers from rat jejunum
1491	Use of a cannulated everted intestinal sac for screening the permeability parameter of drugs
1492	Protein absorption by the intestine of the fetal rat
1493	Absorption of pronase and lysozyme through intestinal mucosa of rabbits
1494	Mechanisms of GI absorption of simifibrate ester in relation to its rate of hydrolysis
1495	Decarboxylation of orally administered levodopa (L-dopa) in the human digestive tract
1496	Transport mechanism of hadacidin and hydroxyurea (carcinostatic compounds) in rat small intestine
1497	Mode of iopanoic acid absorption through the portal venous system of the GI tract of rats
1498	Active transport of thiamine from chick intestine, and competitive inhibition by chloroethylthiamine
1499	Isolation of human epidermal components soluble in dimethyl sulfoxide; possible mechanism of dimethyl sulfoxide action in percutaneous absorption
1500	Mechanism of action of xylene, dimethyl sulfoxide, and di(2-ethylhexyl)amine in skin penetration of drugs
1501	Comparison of drug potency by dermal tissue permeability test on a filter paper implanted subcutaneously in the ventral region of rats
1502	Keratin layer regarded as the major barrier against penicillin penetration through the skin
1503	Penetration of salicylic acid through epidermal barrier of the skin
1504	Time course of cutaneous reservoir in percutaneous absorption of drugs
1505	Corneal endothelium and Descemet's membrane permeability by solutes with varying molecular weights
1506	Influence of various drugs and surfactants on corneal permeability
1507	Biliary excretion of riboflavin found negligible in man
1508	Absorption of sulfobromophthalein (bromsulphthalein) from the biliary system of the rat
1509	Absorption of iodipamide from the biliary system of the rabbit

chloride, a quaternary ammonium drug, were investigated in the dog. Apparent absorption rate constants from the isolated jejunum and ileum were found to be 7.89×10^{-3} and 1.75×10^{-2} min.$^{-1}$, respectively. After oral administration of the drug in solution, detectable plasma levels were obtained in unanesthetized dogs but not in anesthetized dogs. A three-compartment model was employed to describe plasma levels of the drug after intravenous administration (1516).

Methods commonly employed to calculate absorption rate constants from the time course of drug in the blood were shown to yield "apparent" rate constant values when the drug at the site of administration is simultaneously lost to an extravascular compartment(s). It was demonstrated that the true rate constant for absorption in such a case can be calculated by determining the fraction of the dose actually absorbed, provided that all of the initial dose can be accounted for by other simultaneous rate processes (1517). A biokinetic method for the analysis of temporal pharmacological data was described, which permits the computation of the amount of drug absorbed from a site of administration at any time following dosing by any route. This pharmacological approach obviates the need for the periodic sampling of body fluids to determine drug absorption rates (1518). Application of the pharmacological method was demonstrated for two mydriatically active drugs, tropicamide and tridihexethyl chloride, administered ophthalmically, intravenously, intramuscularly, and orally to rabbits (1519). The time course of indomethacin plasma levels in rabbits after intravenous or intraduodenal administration followed a two-compartment model system, but the rate constants estimated by this system increased as the dose was increased, which was ascribed to the saturable binding of the drug to protein (1520). In a subsequent study, the mechanism of intestinal absorption in the rat and drug bioavailability in man after oral administration of micronized indomethacin powder were investigated. Major conclusions derived from the study were: (*a*) indomethacin was bound strongly to the intestinal tissue, (*b*) both the ionized and unionized forms of the drug were absorbed, and (*c*) 96.2% of the drug dose was absorbed in man from capsules containing micronized drug powder (1521).

The absorption of iron was not influenced by concurrent oral administration of ascorbate, succinate, dioctyl sulfosuccinate, fumarate, aspartate, or folate in normal humans or subjects with iron deficiency. Slow-release preparations of ferrous sulfate were only half as active compared to conventional rapid-release dosage forms (1522). Following oral administration of 1–10 mg. sodium fluoride to humans, the peak salivary fluoride concentrations occurred about 45 min. later, with the rate of the subsequent decline being a function of the dose (1523). Copper sulfate has been regarded as a rapidly acting emetic for use in the immediate treatment of poisoning by ingestion. However, in view of the significant oral absorption of copper sulfate observed in rats, its use as an emetic was not recommended (1524). The peak serum levels of lithium in human subjects, after oral administration of a single standard dose of lithium acetate or timed-release tablets of lithium carbonate or lithium sulfate, were attained after 1, 2, and 3 hr., respectively (1525).

The kinetics and equilibrium of hexachlorophene sorption and desorption by human epidermis were studied *in vivo*, utilizing a bioelectrometric technique and direct drug analysis. An average of 41.6% of hexachlorophene was recovered by elutriation from the contents of three apparent kinetic compartments (1526). The *in vitro* penetration of methotrexate through human and hairless mouse skin was determined by scintillation counting and by determining the inhibition of dihydrofolate reductase. Significant absorption of the drug through the skin evidenced by both methods suggested efficacy of methotrexate in dermatology (1527). The fate of disodium cromoglycate in asthmatic patients was examined after oral, inhaled, and intravenous administration. Although maximum plasma concentrations

were obtained within 15 min. of inhaling the drug, which suggests rapid drug absorption from the lung, most inhaled drug was swallowed and excreted in the feces (1528, 1529). In a similar study, absorption and excretion characteristics after oral and inhaled administration of salbutamol to asthmatic patients were investigated (1530).

Additional studies on drug absorption are listed in Table XL.

Pharmacokinetics—General principles of pharmacokinetics, mathematical aspects of single- and multicompartmental models, and application of these concepts to absorption, distribution, metabolism, and excretion studies of a drug as well as to establishment of an optimal dosage scheme were discussed in a number of review articles (1558–1567). In addition, many other reviews focused on pharmacokinetics of specific drugs—*viz.*, niacin (nicotinic acid) and its derivatives (1568); morphine and morphine-like analgesics (1569); hydrochlorothiazide, ioglycamate, and antibiotics (1570); magnesium, plutonium, and iodine (1571); aspirin (1572); penicillin (1573); pentobarbital and penicillin G (1574); and antibiotics (1575). Quantitative and qualitative aspects of pharmacokinetics in relation to biological membrane permeability (1576) and the skin as an organ of absorption from a pharmacokinetic viewpoint (1577) were discussed in two separate reviews.

Earlier pharmacokinetic methods generally assumed the body as a single compartment, with drug absorption and other kinetic processes occurring at first-order rates. A two-compartment model has been proposed, which assumes a central and a peripheral body compartment. An equation for the two-compartment model was derived, which provides interrelationships among absorption, distribution, and elimination processes following oral administration of a drug. These concepts were further applied to study the effect of a solid drug dispersion on the absorption of highly water-insoluble steroids (1578). The two-compartment model assumes that the amount transferred to the peripheral compartment is directly proportional to the dose. A nonlinear model was considered in which the amount of drug transferred to the peripheral compartment is a curvilinear function of dose due to limited drug storage capacity of the peripheral compartment. It was emphasized that several different doses of a drug need to be administered intravenously to elaborate the appropriate pharmacokinetic model (1579). General treatments were presented by which linear mammillary models with elimination from any compartment can be described, utilizing the method of partial fractions for solving Laplace transforms and a multiple-dosing function. The approach was considered relatively simple and applicable in deriving equations for any linear mammillary compartment model with any first-order, zero-order, or impulse input process (1580). A statistical program for the calculation of pharmacokinetic parameters was described. The results of intravenous injection and drug retention experiments were analyzed by this program according to monoexponential or biexponential relationships (1581).

Many therapeutic agents can be applied more predictably and effectively if a constant plasma concentration can be maintained. With the use of a two-compartment open-system model, a method of combining intravenous bolus and continuous infusion was described to calculate the regimen required to reach a predetermined plateau concentration. Application of the method was demonstrated by administration of selected bolus and continuous infusion of theophylline dose regimens to humans (1582). Attainment of desired peak tissue levels of griseofulvin and aspirin required significantly higher peak plasma levels with a multiple intravenous

Table XL—Additional References on Drug Absorption

Reference	Topic
1531	Review describing chemistry, absorption, distribution, and excretion of digitoxin, digoxin, and ouabain
1532	Absorption and metabolism of tritium-labeled factor M_1 of staphylamycin (virginiamycin) by oral and parenteral administration
1533	Comparison of intestinal absorption, lymph and plasma transport, and tissue uptake of α- and γ-tocopherols in the rat
1534	Review describing absorption of folic acid in man
1535	Absorption, distribution, and excretion of levodopa (L-dopa) in mice and uptake into the cat corpus striatum
1536	Absorption, distribution, and excretion of chlorophenothane in rats after oral and intraperitoneal administration
1537	Measurement of enteric absorption rate using a double tracer technique
1538	Plasma levels of nitroglycerin in man after buccal administration
1539	Absorption, distribution, and excretion of the antiparkinsonian drug 6,6,9-trimethyl-9-azabicyclo-[3.3.1]non-3β-yl-α,α-di(2-thienyl)glycolate hydrochloride monohydrate in mice
1540	Uptake of anti-Rh immunoglobulin after intramuscular and subcutaneous injection
1541	Absorption of sodium hydroxybutyrate in man faster from suppositories than from oral dosage forms
1542	Comparable serum levels of sulfathiazole (norsulfazole) obtained by intravenous injection or rectal suppository
1543	Absorption of potassium phenoxymethyl penicillin in man following oral administration of tablet or solution dosage
1544	Human serum and tissue concentrations of erythromycin stearate and erythromycin estolate after oral administration
1545	Comparison of absorption and excretion after oral administration of erythromycin stearate and erythromycin estolate
1546	Absorption, transport, and biotransformation of methyl salicylate in the dog
1547	GI absorption and excretion of aspirin in rats from ethylcellulose-coated tablets
1548	Absorption and physiologial disposition of fenoprofen in man after oral and intravenous administration
1549	Dose-dependent elimination of propranolol during oral absorption in man
1550	Absorption of kanamycin from respiratory organs
1551	Percutaneous absorption of zinc oxide ointment through rabbit skin
1552	Review of pharmacodynamics of absorption and elimination of inhalation anesthetics
1553	Percutaneous absorption of salicylic acid and carbinoxamine; time course of cutaneous reservoir of drugs
1554	Ocular uptake and kinetics of orally administered osmotic agent, isosorbide, in rabbits
1555	Ascorbic acid absorption in man; pharmacokinetic implications
1556	Absorption kinetics of aspirin in man following oral administration of an aqueous solution
1557	Absorption, distribution, and elimination of fenfluramine and its main metabolite in man

Table XLI—Additional References on Pharmacokinetics

Reference	Topic
1602	Plasma levels and pharmacokinetics of pralidoxime methanesulfonate after oral administration to man
1603	Pharmacokinetics and metabolism of diphenoxylate in man
1604	Effect of renal failure and hemodialysis on cephacetrile pharmacokinetics
1605	Kinetics of some pyrazole derivatives in the rat
1606	Pharmacokinetic study of fatty acid esters of polyethylene glycols
1607	Pharmacokinetics of iopanoic acid metabolism
1608	Comparative pharmacokinetics of daunomycin and adriamycin in several animal species
1609	Pharmacokinetics of colloidal gold-198 after intraarticular and intravenous administration in rabbits and rats
1610	Intravascular retention, dispersal, excretion, and breakdown of gelatin plasma substitutes
1611	Comparative studies on the velocity of the elimination of plasma substitutes by the rabbit
1612	Pharmacokinetics of fentanyl in rabbits in view of the importance for limiting the effect
1613	Pharmacokinetics of escin in mice and rats
1614	Biological half-life of 47.1 hr. for phenobarbital in human babies (about 50% greater in adults)
1615	Pharmacokinetic studies of minoxidil in hypertensive patients
1616	Pharmacokinetics of theophylline; application to adjust clinical dose of aminophylline
1617	Correlation of plasma levels of 4,5-bis(*p*-methoxyphenyl)-2-phenylpyrrole-3-acetonitrile with antiinflammatory activity in polyarthritic rats
1618	Volume of distribution and half-life of heparin after intravenous administration
1619	Pharmacokinetic characteristics of 14-hydroxydaunomycin, an antitumor drug
1620	Comparative pharmcokinetic studies on fenoterol hydrobromide in the rat, dog, and man
1621	Effect of volume of distribution on plasma levels of total radioactivity
1622	Methods of *in vitro* pharmacokinetic investigation of drugs classified as static and dynamic methods
1623	Dynamic *in vitro* method used to study pharmacokinetic characteristics of drugs
1624	Review concerning the effect of distribution, complexing, and pH on pharmacokinetic aspects of drugs
1625	Correlations of pKa and lipid solubility of some tobacco alkaloids with urine excretion in man
1626	Pharmacokinetics of a mixture of chloramphenicol and rifampin (rifampicin) in rats
1627	Relation between the biliary excretion behavior and the elimination from plasma of xanthene dyes and sulfobromophthalein (bromsulphthalein) in the rat
1628	Relation between the renal elimination rate constant of a drug and the urinary flow rate described by a theoretical model
1629	Pharmacokinetics, metabolism, and excretion of alphaprodine in dogs
1630	Plasma urea kinetics in patients treated with an infusion of 30% urea–10% invert sugar solution
1631	Use of hydrolytic rate constants to study glutethimide and its metabolite in human serum
1632	*In vitro* hydrolysis rates of methanesulfonic acid derivatives of sulfonamides compared with pharmacokinetic parameters in rabbits
1633	Integral coefficients of multicompartmental pharmacokinetic models related to chemotherapy
1634	Influence of replacement of *N*-ethyl group by cyanoethyl group on pharmacokinetic parameters of ethylamphetamine in man
1635	Individual differences in the plasma half-lives of lipid-soluble drugs in man
1636	Determination of pharmacokinetic parameters for rapid and slow acetylators of sulfamethazine (sulfadimidine)
1637	Review of the biopharmaceutical applications and factors affecting the biological half-life of drugs
1638	Estimation of plasma concentration following oral administration of a timed-release preparation utilizing a one-compartment open-model system
1639	Pharmacokinetic profile of sulfisoxazole following intravenous, intramuscular, and oral administration to man
1640	Effect of protein binding on the pharmacokinetics of sulfanilamides in rats
1641	Disappearance rate of exogenous gastrin in dogs analyzed by a nonlinear curve-fitting computer program
1642	Simulation of pharmacokinetics of cyproterone acetate by analog computer
1643	Pharmacokinetic models for methotrexate and 1-β-D-arabinofuranosylcytosine
1644	Mathematical models simulating pharmacokinetic parameters of methotrexate and of DNA biosynthesis
1645	Plasma half-lives of the enantiomers of warfarin in drug-resistant and drug-susceptible rats
1646	Plasma half-lives and pharmacological effects of the enantiomers of warfarin in rats
1647	Effects of protein binding of drugs on areas under plasma concentration–time curves
1648	Effect of halofenate on protein binding of other drugs and on plasma half-life of antipyrine in monkeys
1649	Pharmacokinetics of phenylbutazone, pentobarbital, antipyrine, sulfanilamide, quinine, and tolazoline in the goat

dosing regimen than with continuous infusion. Thus, infusion therapy was preferred, especially with relatively toxic drugs, when appearance of the drug in a peripheral compartment was a desired consequence of therapy (1583). Relationships between the dose and plateau levels of drugs eliminated by parallel first-order and capacity-limited kinetics were derived by Tsuchiya and Levy (1584). The authors concluded that repetitive administration at constant time intervals of fixed doses of drugs that are eliminated by apparent first-order kinetics usually results in the eventual attainment of a drug level plateau in the body. If a drug is eliminated solely by capacity-limited kinetics in the therapeutic dose range, it accumulates in the body without limit when the dose exceeds a certain amount (1584). Derivation of theoretical relationships useful for the characterization of multiple-dosing pharmacokinetics of hypoprothrombinemic anticoagulant drugs and the computation of optimum dosing regimens for individual patients was presented (1585).

Various parameters of the two-compartment open model were classified into three groups, depending upon how these parameters are influenced by a change induced in the elimination constant. At a given dose of drug, certain parameters are independent of the elimination constant, others change exactly in proportion to the elimination constant, while a third group is nonlinear or hybrid parameters (1586). A relationship between drug distribution and elimination in multicompartment systems was presented, which suggested that under certain conditions a decrease in the elimination rate constant results in a significant decrease in the apparent volume of distribution. The implication of a change in the apparent volume of distribution with respect to dose–response relationships, estimation of bioavailability, absorption rate, *etc.*, was considered (1587). An unusual

example of nonlinear, dose-dependent pharmacokinetics was observed in the case of riboflavin absorption and excretion in the rat. The elimination of the vitamin was shown to involve at least two nonlinear processes occurring simultaneously. One process involved biliary excretion which increased disproportionately with increasing body levels of riboflavin; the other process appeared to be a binding of the vitamin to tissues which function kinetically as deep compartments. Over the dose range studied, the nonlinear tissue-binding phenomenon was predominant over the nonlinear biliary excretion in riboflavin-deficient rats. The converse was true in the normal, nondeficient animal (1588).

The biliary excretion of intravenously administered methyl orange and its metabolites by rats was used to illustrate a one-compartment model in which a drug underwent two successive metabolic reactions. Data were analyzed graphically and with a computer program to estimate successive metabolic rates and the rate of biliary excretion (1589). Graphical analysis of the curves of biliary concentration as a function of time and the rate constants obtained after intravenous injection of fenpentadiol in rats indicated that the system may be represented by a two-compartment open model. Comparison of the pharmacokinetic parameters of biliary excretion with those of the enterohepatic cycle showed that the total elimination period is shortened if excretion occurs without the cycle. Half of the injected dose was observed to undergo total elimination within 1 hr., and 47% was excreted by the biliary route within 2.5 hr. (1590).

A pharmacokinetic model for the distribution and elimination of tubocurarine in man was presented, which represented the body as a three-compartment linear system with the site of drug action located in the central compartment. The decline in neuromuscular blocking effect with increasing dose elicited by tubocurarine was in accordance with the pharmacokinetic characteristics of a multicompartment system (1591, 1592). The distribution kinetics of inulin and urea were studied in the rat to test the validity of a proposed compartmental model. An open two-compartment model provided valid parameters for inulin data, while a three-compartment model fit the urea data (1593). The time course of rifampin (rifampicin) concentration in the serum, bile, and urine was determined in patients after oral administration of the drug. The results were interpreted on the basis of a four-compartment model consisting of intestine, blood, bile, and urine compartments (1594).

The pharmacokinetics of methylene blue, representative of highly ionized drugs, was investigated in the rat, dog, and man by DiSanto and Wagner (1595–1597). The authors concluded that methylene blue is well absorbed in man but poorly absorbed in the dog after oral administration. Plasma concentration–time data obtained from intravenous injection of methylene blue to a dog seemed to fit a linear two-compartment open model; the results of drug concentrations in the lung, liver, kidney, and heart tissues of rats after intravenous injection, with respect to dose, were shown to fit the nonlinear heterogeneous one-compartment open model (1595–1597). The blood level–time relationships for sulfamethazine, sulfisomidine, and sulfathiazole were determined in rabbits after intravenous injection. The results were fitted to a two-compartment open model, and the model parameters were obtained. Differences between drugs, animals, and treatments were studied in terms of urinary and metabolic rate constants, intercompartment diffusion constants, and clearance values (1598). In a similar study comparing pharmacokinetic parameters of sulfanilic acid and 1-naphthylamine-4-sulfonic acid, it was concluded that the latter compound is actively secreted into the renal tubule while the former is not (1599).

Computer simulations were used to determine suitable experimental conditions for distinguishing between a recently developed pharmacokinetic model for salicylate elimination (involving saturable salicyl phenolic glucuronide formation) and a previously proposed model (based on the assumption that the syntheses of salicyl phenolic and acyl glucuronides are apparent first-order processes). Studies in man according to the computer-simulated experimental design confirmed the new pharmacokinetic model, which provided further evidence that man has a limited capacity to form salicyl phenolic glucuronide (1600, 1601).

Additional references on pharmacokinetics are listed in Table XLI.

REFERENCES

(850) G. L. Flynn and R. W. Smith, *J. Pharm. Sci.*, **61**, 61 (1972).

(851) G. L. Flynn and S. H. Yalkowsky, *ibid.*, **61**, 838(1972).

(852) G. L. Flynn, O. S. Carpenter, and S. H. Yalkowsky, *ibid.*, **61**, 312(1972).

(853) C. F. Most, *J. Biomed. Mater. Res.*, **6**, 3(1972); through *Chem. Abstr.*, **76**, 90000w(1972).

(854) D. G. Serota, M. C. Meyer, and J. Autian, *J. Pharm. Sci.*, **61**, 416(1972).

(855) K. Nasim, M. C. Meyer, and J. Autian, *ibid.*, **61**, 1775 (1972).

(856) G. W. C. Hung and J. Autian, *ibid.*, **61**, 1094(1972).

(857) C. W. Woodruff, G. E. Peck, and G. S. Banker, *ibid.*, **61**, 1956(1972).

(858) J. Swarbrick, A. H. Amann, and R. E. Lindstrom, *ibid.*, **61**, 1645(1972).

(859) D. J. Allen, J. D. DeMarco, and K. C. Kwan, *ibid.*, **61**, 106(1972).

(860) R. E. Beck and J. S. Schultz, *Biochim. Biophys. Acta*, **255**, 273(1972); through *Chem. Abstr.*, **76**, 90518w(1972).

(861) T. Conlon and B. Craven, *Aust. J. Chem.*, **25**, 695(1972); through *Chem. Abstr.*, **76**, 117821d(1972).

(862) G. S. Manning, *J. Phys. Chem.*, **76**, 393(1972); through *Chem. Abstr.*, **76**, 76960c(1972).

(863) M. Nakagaki and M. Yonese, *Yakugaku Zasshi*, **91**, 1211 (1971).

(864) M. Nakagaki and M. Kobayashi, *ibid.*, **92**, 1212(1972).

(865) M. Yonese, *Nagoya Shiritsu Daigaku Yakugakubu Kenkyu Nempo*, **19**, 48(1971); through *Chem. Abstr.*, **77**, 156722n(1972).

(866) H. Levitan and J. L. Barker, *Science*, **178**, 63(1972).

(867) *Ibid.*, **176**, 1423(1972).

(868) V. H. Cohn, *Fundam. Drug Metab. Drug Disposition*, **1971**, 3; through *Chem. Abstr.*, **77**, 96670g(1972).

(869) M. Blank, *Tech. Surface Colloid Chem. Phys.*, **1**, 41 (1972); through *Chem. Abstr.*, **77**, 169073b(1972).

(870) R. Lefaux, *Labo-Pharma-Probl. Tech.*, **19**, 55(1971); through *Chem. Abstr.*, **76**, 89973j(1972).

(871) R. Lefaux, *Pharma Int., Engl. Ed.*, No. 4, 5(1971); through *Chem. Abstr.*, **76**, 76389y(1972).

(872) A. Chiolle, *Mater. Plast. Elastomeri*, **37**, 1183(1971); through *Chem. Abstr.*, **76**, 76797e(1972).

(873) J. T. Edward, *Intestinal Absorption Metal Ions, Trace Elem. Radionuclides*, **1971**, 3; through *Chem. Abstr.*, **76**, 82278c (1972).

(874) J. J. Sciarra and R. N. Gidwani, *J. Pharm. Sci.*, **61**, 754 (1972).

(875) G. Baum, *J. Phys. Chem.*, **76**, 1872(1972); through *Chem. Abstr.*, **77**, 52624r(1972).

(876) H. Hauser, M. C. Phillips, and M. Stubbs, *Nature*, **239**, 342(1972).

(877) B. E. Cohen and A. D. Bangham, *ibid.*, **236**, 173(1972).

(878) K. Takamura, M. Koishi, and T. Kondo, *Kolloid-Z. Z. Polym.*, **248**, 929(1971); through *Chem. Abstr.*, **76**, 76403y(1972).

(879) W. D. Wosilait and S. Garten, *Res. Commun. Chem., Pathol. Pharmacol.*, **3**, 535(1972); through *Chem. Abstr.*, **77**, 56506b (1972).

(880) A. Agren, R. Elofsson, and S. O. Nilsson, *Acta Pharmacol. Toxicol. Suppl.*, **29**, 48(1971); through *Chem. Abstr.*, **76**, 121538j(1972).

(881) R. Elofsson, S. O. Nilsson, and B. Kluczykowska, *Acta Pharm. Suecica*, **8**, 465(1971); through *Chem. Abstr.*, **76**, 81340e (1972).

(882) A. Agren, R. Elofsson, and S. O. Nilsson, *ibid.*, **8**, 475 (1971); through *Chem. Abstr.*, **76**, 80991f(1972).

(883) J. N. Costanzo, Z. N. Gaut, J. T. Benedict, and H. M. Solomon, *Pharmacology*, **6**, 164(1971); through *Chem. Abstr.*, **76**, 148696w(1972).

(884) T. Fujita, *J. Med. Chem.*, **15**, 1049(1972).

(885) J. M. Vandenbelt, C. Hansch, and C. Church, *ibid.*, **15**, 787(1972).

(886) W. G. Unger, *J. Pharm. Pharmacol.*, **24**, 470(1972).

(887) D. C. Evered, *Eur. J. Pharmacol.*, **18**, 236(1972); through *Chem. Abstr.*, **77**, 56473p(1972).

(888) J. E. Doherty, W. H. Hall, J. Sherwood, D. Girkin, and J. Gammill, *Amer. J. Cardiol.*, **28**, 326(1971); through *Chem. Abstr.*, **76**, 94442q(1972).

(889) K. M. Lunde, *Acta Pharmacol. Toxicol., Suppl.*, **29**, 152 (1971); through *Chem. Abstr.*, **76**, 121919j(1972).

(890) H. E. Rosenthal, E. Pietrzak, W. R. Slaunwhite, Jr., and A. A. Sandberg, *J. Clin. Endocrinol. Metab.*, **34**, 805(1972).

(891) S. Keresztes-Nagy, R. F. Mais, Y. T. Oester, and J. F. Zaroslinski, *Anal. Biochem.*, **48**, 80(1972); through *Chem. Abstr.*, **77**, 56309q(1972).

(892) R. Spector, D. T. Korkin, and A. V. Lorenzo, *J. Pharm. Pharmacol.*, **24**, 786(1972).

(893) K. Splinter and H. Ankermann, *Zentralbl. Pharm., Pharmakotherapie Laboratoriumsdiagnostik*, **110**, 1273(1971); through *Chem. Abstr.*, **76**, 135535q(1972).

(894) J. Judis, *J. Pharm. Sci.*, **61**, 89(1972).

(895) G. Pagnini, F. DiCarlo, S. Agozzino, and D. Pagnini, *J. Pharm. Pharmacol.*, **24**, 981(1972).

(896) I. Yagi, Y. Ohsawa, S. Tsutsumi, Y. Gidoh, and K. Nakamura, *Repura*, **39**, 246(1970); through *Chem. Abstr.*, **76**, 94833t (1972).

(897) S. Tsutsumi, Y. Sakamoto, K. Nakamura, M. Abe, F. Minagawa, Y. Yoshino, Y. Ohsawa, and T. Sato, *ibid.*, **39**, 179 (1970); through *Chem. Abstr.*, **76**, 94866f(1972).

(898) W. Pache, D. Chapman, and R. Hillaby, *Biochim. Biophys. Acta*, **255**, 358(1972); through *Chem. Abstr.*, **76**, 135565c (1972).

(899) W. Pache and D. Chapman, *ibid.*, **255**, 348(1972); through *Chem. Abstr.*, **76**, 135564b(1972).

(900) A. Felmeister, D. Tsai, and N. D. Weiner, *J. Pharm. Sci.*, **61**, 1065(1972).

(901) N. D. Weiner, M. Y. Lu, and M. Rosoff, *ibid.*, **61**, 1098 (1972).

(902) A. T. Florence and R. Rahman, *J. Pharm. Pharmacol.*, **24**, 943(1972).

(903) P. K. Knoefel, *Int. Encycl. Pharmacol. Ther.*, **76**, 133(1971); through *Chem. Abstr.*, **77**, 159934u(1972).

(904) H. Turakka, *Farm. Aikak.*, **80**, 313(1971); through *Chem. Abstr.*, **76**, 94360m(1972).

(905) Y. Cohen, *Int. Encycl. Pharmacol. Ther.*, **78**, 241(1971); through *Chem. Abstr.*, **76**, 135402x(1972).

(906) S. Gorog and M. Beck, *Magy, Kem. Lapja*, **27**, 260(1972); through *Chem. Abstr.*, **77**, 159945y(1972).

(907) C. F. Chignell, *Methods Pharmacol.*, **2**, 33(1972); through *Chem. Abstr.*, **77**, 69890x(1972).

(908) N. Nambu and T. Nagai, *Chem. Pharm. Bull.*, **20**, 2463 (1972).

(909) J. H. Perrin, D. A. Nelson, and I. B. Tyson, *J. Pharm. Sci.*, **61**, 1667(1972).

(910) J. S. Crawford, R. L. Jones, J. M. Thompson, and W. D. Wells, *Brit. J. Pharmacol.*, **44**, 80(1972); through *Chem. Abstr.*, **76**, 135486c(1972).

(911) J. T. Stewart and J. L. Story, *J. Pharm. Sci.*, **61**, 652(1972).

(912) F. A. Suso and H. M. Edwards, *Nature*, **236**, 230(1972).

(913) W. S. Tolgyesi and E. M. Cottington, *Appl. Polym. Symp., No. 18*, **1971**, 735; through *Chem. Abstr.*, **76**, 37343j(1972).

(914) K. I. Bender, *Tr. Saratov. Med. Inst.*, **70**, 156(1970); through *Chem. Abstr.*, **77**, 160229z(1972).

(915) C. T. Plessas, *Chem. Chron. Genike Ekdosis*, **37**, 8(1972); through *Chem. Abstr.*, **77**, 43092p(1972).

(916) G. I. Grishin, *Tr. Leningrad. Khim.-Farm. Inst.*, **27**, 113 (1969); through *Chem. Abstr.*, **76**, 89985q(1972).

(917) E. Menczel and H. I. Maibach, *Acta Dermato-Venereol.*, **52**, 38(1972); through *Chem. Abstr.*, **76**, 95309p(1972).

(918) S. W. Spaulding and R. I. Gregerman, *J. Clin. Endocrinol. Metab.*, **34**, 974(1972).

(919) A. M. Green, J. S. Marshall, J. Pensky, and J. B. Stanbury, *Science*, **175**, 1378(1972).

(920) P. G. Popov, K. I. Vaptsarova, G. P. Kosekova, and T. K. Nikolov, *Dokl. Bolg. Akad. Nauk*, **24**, 1501(1971); through *Chem. Abstr.*, **76**, 148816k(1972).

(921) T. Perenyi, L. Biro, M. Arr, E. K. Novak, S. Szoke, and L. Fever, *Acta Pharm. Hung.*, **41**, 247(1971); through *Chem. Abstr.*, **76**, 135533r(1972).

(922) M. Barza, H. Vine, and L. Weinstein, *Antimicrob. Ag. Chemother.*, **1**, 427(1972); through *Chem. Abstr.*, **77**, 56480p(1972).

(923) I. Moriguchi, S. Fushimi, R. Umehara, and N. Kaneniwa, *Chem. Pharm. Bull.*, **20**, 834(1972).

(924) J. D. Baggot, L. E. Davis, and C. A. Neff, *Biochem. Pharmacol.*, **21**, 1813(1972).

(925) J. O. Branstad, U. Meresaar, and A. Agren, *Acta Pharm. Suecica*, **9**, 129(1972); through *Chem. Abstr.*, **77**, 43153j(1972).

(926) H. W. Jun, L. A. Luzzi, and P. L. Hsu, *J. Pharm. Sci.*, **61**, 1835(1972).

(927) G. L. Amidon, *Diss. Abstr., Int. B*, **32**, 4034(1972).

(928) I. Moriguchi, S. Fushimi, and N. Kaneniwa, *Chem. Pharm. Bull.*, **20**, 258(1972).

(929) *Ibid.*, **20**, 411(1972).

(930) E. R. Garrett and D. J. Weber, *J. Pharm. Sci.*, **61**, 1241 (1972).

(931) W. O. Foye and J. Lo, *ibid.*, **61**, 1209(1972).

(932) Y. Kidani, R. Saito, and H. Koike, *Yakugaku Zasshi*, **92**, 1063(1972).

(933) J. S. G. Cox, G. R. Kennedy, J. King, P. R. Marshall, and D. Rutherford, *J. Pharm. Pharmacol.*, **24**, 513(1972).

(934) B. W. Barry and G. F. J. Russell, *J. Pharm. Sci.*, **61**, 502 (1972).

(935) Y. P. Chow and A. J. Repta, *ibid.*, **61**, 1454(1972).

(936) C. Dearden, *ibid.*, **61**, 1661(1972).

(937) R. M. E. Richards, A. F. Fell, and J. M. E. Butchart, *J. Pharm. Pharmacol.*, **24**, 999(1972).

(938) J. C. Smith, J. W. Clitherow, and W. Marlow, *ibid.*, **24**, 111P(1972).

(939) P. R. Andrews, *J. Pharm. Sci.*, **61**, 1717(1972).

(940) A. L. Thakkar, P. B. Kuehn, J. H. Perrin, and W. L. Wilham, *ibid.*, **61**, 1841(1972).

(941) K. Koisumi and K. Fujimura, *Yakugaku Zasshi*, **92**, 32 (1972).

(942) M. Nakagaki and S. Shimabayashi, *Nippon Kagaku Kaishi*, **8**, 1496(1972); through *Chem. Abstr.*, **77**, 166499j(1972).

(943) J. I. Zatz, *J. Pharm. Sci.*, **61**, 977(1972).

(944) S. Leucuta, *Farmacia (Bucharest)*, **20**, 221(1972); through *Chem. Abstr.*, **77**, 52259a(1972).

(945) K. Bolewski and T. Tomaszkiewicz, *Farm. Pol.*, **27**, 773 (1971); through *Chem. Abstr.*, **76**, 49837m(1972).

(946) K. Bolewski and H. Nalewajko, *ibid.*, **28**, 19(1972); through *Chem. Abstr.*, **76**, 158264t(1972).

(947) I. H. Stockley, *Pharm. J.*, **209**, 105(1972); through *Chem. Abstr.*, **77**, 147377b(1972).

(948) P. Rohdewald, *Pharm. Ztg.*, **117**, 251(1972); through *Chem. Abstr.*, **77**, 39183b(1972).

(949) J. Jacobs, R. A. Anderson, and T. R. Watson, *J. Pharm.*

Pharmacol., **24**, 586(1972).

(950) S. G. Schulman and K. Abate, *J. Pharm. Sci.*, **61**, 1576 (1972).

(951) J. H. Perrin, W. L. Wilham, and A. L. Thakkar, *J. Pharm. Pharmacol.*, **24**, 257(1972).

(952) M. E. Nimni, *Biochem. Pharmacol.*, **21**, 485(1972); through *Chem. Abstr.*, **76**, 149215a(1972).

(953) N. H. Choulis, *J. Pharm. Sci.*, **61**, 293(1972).

(954) *Ibid.*, **61**, 1325(1972).

(955) L. V. Dmitrienki, E. B. Vulikh, and G. V. Samsonov, *Izv. Akad. Nauk SSSR, Ser. Khim.* (3) **1972**, 730; through *Chem. Abstr.*, **77**, 39126k(1972).

(956) M. K. Youssef and A. A. Kassem, *Bull. Fac. Pharm. Cairo Univ.*, **9**, 1(1970); through *Chem. Abstr.*, **77**, 39116g(1972).

(957) L. V. Khazhakyan, N. L. Luk'yanenko, R. K. Aliev, and G. A. Gevorkyan, *Arm. Khim. Zh.*, **25**, 476(1972); through *Chem. Abstr.*, **77**, 160006z(1972).

(958) Y. Matsushima and S. Akaboshi, *J. Radiat. Res.*, **12**, 37 (1971); through *Chem. Abstr.*, **76**, 30674j(1972).

(959) M. Nakagaki and M. Kobayashi, *Yakugaku Zasshi*, **92**, 1204(1972).

(960) P. C. Manor and W. Saenger, *Nature*, **237**, 392(1972).

(961) M. M. Brewer and I. D. Robb, *Chem. Ind.*, No. 13, 530 (1972).

(962) S. M. Blaug and W. Huang, *J. Pharm. Sci.*, **61**, 1770(1972).

(963) S. Tarjanyi, G. Liptay, and M. Igloy, *Proc. Conf. Appl. Phys. Chem., 2nd*, **1**, 271(1971); through *Chem. Abstr.*, **76**, 103698g (1972).

(964) V. V. Pavlov, *Fiz. Khim. Poverkh. Yavlenii Rasplavakh*, **1971**, 14; through *Chem. Abstr.*, **77**, 52611j(1972).

(965) M. V. Berry, R. F. Durrans, and R. Evans, *J. Phys. A*, **5**, 166(1971); through *Chem. Abstr.*, **76**, 63631w(1972).

(966) J. C. Bonnet and F. P. Pike, *J. Chem. Eng. Data*, **17**, 145(1972); through *Chem. Abstr.*, **76**, 145207b(1972).

(967) B. Swaroop, *Proc. Nat. Acad. Sci., India, Sect. A*, **41**, 121(1971); through *Chem. Abstr.*, **77**, 118585n(1972).

(968) R. Defay, A. Sanfeld, and A. Steinchen, *J. Chim. Phys. Physicochim. Biol.*, **69**, 1374(1972); through *Chem. Abstr.*, **77**, 156675z(1972).

(969) *Ibid.*, **69**, 1380(1972); through *Chem. Abstr.*, **77**, 156676a (1972).

(970) N. L. Gershfeld and R. E. Pagano, *J. Phys. Chem.*, **76**, 1231(1972).

(971) *Ibid.*, **76**, 1244(1972).

(972) N. Kuramoto, K. Sekita, K. Motomura, M. Nakamura, and R. Matuura, *Mem. Fac. Sci., Kyushu Univ., Ser. C*, **8**, 67 (1972); through *Chem. Abstr.*, **76**, 145204y(1972).

(973) S. Baykut and M. Tuncay, *Istanbul Univ. Fen Fak. Mecm., Seri C*, **34**, 1(1969); through *Chem. Abstr.*, **76**, 158675c(1972).

(974) M. Nakagaki, N. Funasaki, and K. Fujita, *Nippon Kagaku Kaishi*, (2) 243(1972); through *Chem. Abstr.*, **76**, 104123c(1972).

(975) D. Kunath, A. Reklat, and K. H. Roedel, *Z. Phys. Chem. (Leipzig)*, **249**, 202(1972); through *Chem. Abstr.*, **77**, 39598r(1972).

(976) J. W. Munden, *Diss. Abstr., Int. B*, **33**, 2677(1972).

(977) F. A. Vilallonga, E. R. Garrett, and M. Cereijido, *J. Pharm. Sci.*, **61**, 1720(1972).

(978) M. Harada, T. Imamura, and H. Eguchi, *Kyoto Daigaku Kogaku Kenkyusho Iho*, **40**, 43(1971); through *Chem. Abstr.*, **77**, 169090e(1972).

(979) J. H. Clint, J. M. Corkill, J. F. Goodman, and J. R. Tate, *Hydrophobic Surfaces, Kendall Award Symp.*, **5**, 180(1968); through *Chem. Abstr.*, **76**, 76809k(1972).

(980) I. P. Vyrodov, *Fiz. Khim. Poverkh. Yavlenii Vys. Temp.*, **1971**, 154; through *Chem. Abstr.*, **77**, 39561y(1972).

(981) A. I. Rusanov, *Progr. Surface Membrane Sci.*, **4**, 57(1971); through *Chem. Abstr.*, **77**, 105814m(1972).

(982) H. D. Doerfler, *Wiss. Z. Martin-Luther-Univ., Halle-Wittenberg, Math.-Naturwiss. Reihe*, **21**, 69(1972); through *Chem. Abstr.*, **77**, 52622p(1972).

(983) H. Sawistowski, *Recent Advan. Liquid-Liquid Extr.*, **1971**, 293; through *Chem. Abstr.*, **76**, 158662w(1972).

(984) K. Tsutsumi and H. Takahashi, *Seisan-Kenkyu*, **23**, 368 (1971); through *Chem. Abstr.*, **76**, 63617w(1972).

(985) M. Terzi, *Stud. Cercet. Chim.*, **19**, 875(1971); through *Chem. Abstr.*, **76**, 50360g(1972).

(986) M. Aratani, *Hyomen*, **10**, 99(1972); through *Chem. Abstr.*, **77**, 166501d(1972).

(987) N. L. Gershfeld, *Tech. Surface Colloid Chem. Phys.*, **1**, 1(1972); through *Chem. Abstr.*, **77**, 169072a(1972).

(988) H. Wagenbreth, *Mineraloele Verw. Prod., 2. Auflage*, **1**, 21(1969); through *Chem. Abstr.*, **77**, 169077f(1972).

(989) K. C. Jain, S. S. Solanki, and V. R. Shastry, *Vijnana Parishad Anusandhan Patrika*, **14**, 49(1971); through *Chem. Abstr.*, **77**, 9880j(1972).

(990) H. Schott, *Amer. J. Pharm. Educ.*, **36**, 232(1972).

(991) N. D. Weiner, P. Noomnont, and A. Felmeister, *J. Lipid Res.*, **13**, 253(1972); through *Chem. Abstr.*, **76**, 131429p(1972).

(992) S. I. Popel and V. V. Pavlov, *Fiz. Khim. Poverkh. Yavlenii Vys. Temp.*, **1971**, 16; through *Chem. Abstr.*, **77**, 118576k(1972).

(993) J. C. Berg, *U. S. Office Saline Water, Res. Develop. Progr. Rep.*, No. 724, (1971); through *Chem. Abstr.*, **76**, 158680a(1972).

(994) B. N. Ghosh, *J. Indian Chem. Soc.*, **48**, 561(1971); through *Chem. Abstr.*, **76**, 74073s(1972).

(995) W. Noll, H. Steinbach, and C. Sucker, *J. Polym. Sci., Part C*, No. 34, 123(1971); through *Chem. Abstr.*, **76**, 26655m (1972).

(996) D. J. Cotton, *Phil. Mag.*, **25**, 77(1972); through *Chem. Abstr.*, **76**, 63750j(1972).

(997) S. Levine and K. Robinson, *J. Phys. Chem.*, **76**, 876(1972); through *Chem. Abstr.*, **76**, 117783t(1972).

(998) K. G. McCurdy and B. P. Erno, *Can. J. Chem.*, **50**, 701 (1972).

(999) E. L. Rowe, *J. Pharm. Sci.*, **61**, 2423(1972).

(1000) V. F. Yakovlev, *Zh. Fiz. Khim*, **46**, 1234(1972); through *Chem. Abstr.*, **77**, 105825r(1972).

(1001) S. Sircar, J. Novosad, and A. L. Myers, *Ind. Eng. Chem., Fundam.*, **11**, 249(1972); through *Chem. Abstr.*, **76**, 145272u(1972).

(1002) A. I. Vitvitskii, *Zh. Fiz. Chim.*, **45**, 2620(1971); through *Chem. Abstr.*, **76**, 37705d(1972).

(1003) B. Waligora and D. Goralczyk, *Bull. Acad. Pol. Sci., Ser. Sci. Chim.*, **19**, 465(1971); through *Chem. Abstr.*, **76**, 76812f(1972).

(1004) A. G. Bois, J. F. Baret, and R. Roux, *Kolloid-Z. Z. Polym.*, **249**, 1144(1971); through *Chem. Abstr.*, **76**, 131832q(1972).

(1005) J. T. Carstensen and K. S. E. Su, *J. Pharm. Sci.*, **61**, 139 (1972).

(1006) K. S. E. Su and J. T. Carstensen, *ibid.*, **61**, 420(1972).

(1007) J. W. McGinity, *Diss. Abst., Int. B*, **33**, 1643(1972).

(1008) N. Lahav and S. Raziel, *Isr. J. Chem.*, **9**, 683(1971); through *Chem. Abstr.*, **76**, 145280v(1972).

(1009) W. L. German and D. A. Harding, *Clay Miner.*, **9**, 167 (1971); through *Chem. Abstr.*, **76**, 90519x(1972).

(1010) V. Y. Tretinnik, V. V. Parkhomenko, N. N. Kruglitskii, A. S. Novotorov, and L. A. Kudra, *Ukr. Khim. Zh.*, **38**, 256(1972); through *Chem. Abstr.*, **77**, 10046y(1972).

(1011) D. N. Ghosal and S. K. Mukherjee, *J. Indian Chem. Soc.*, **49**, 569(1972); through *Chem. Abstr.*, **77**, 118699c(1972).

(1012) C. D. Clarke and N. A. Armstrong, *Pharm. J.*, **209**, 44 (1972).

(1013) P. W. Stern, *Diss. Abstr., Int. B*, **32**, 6319(1972).

(1014) J. Ivan, *Acta Pharm. Hung.*, **42**, 97(1972); through *Chem. Abstr.*, **77**, 52275c(1972).

(1015) P. Balatre, J. C. Guyot, J. Mulleman, and M. Traisnel, *J. Pharm. Belg.*, **26**, 539(1971); through *Chem. Abstr.*, **76**, 49893b (1972).

(1016) A. Gamot, N. Guisez, J. Mulleman, and M. Traisnel, *ibid.*, **26**, 548(1971); through *Chem. Abstr.*, **76**, 49895d(1972).

(1017) A. V. Kiselev, *Hydrophobic Surfaces, Kendell Award Symp.*, **5**, 88(1968); through *Chem. Abstr.*, **76**, 76803d(1972).

(1018) S. Ross, *Progr. Surface Membrane Sci.*, **4**, 377(1971); through *Chem. Abstr.*, **77**, 105812j(1972).

(1019) D. J. Schiffrin, *Electrochemistry*, **1**, 223(1968–69); through *Chem. Abstr.*, **76**, 63615u(1972).

(1020) E. I. Kotov, *Teor. Prikl. Probl. Rasseyan, Svela*, **1971**, 387; through *Chem. Abstr.*, **77**, 52628v(1972).

(1021) I. Panaiotov and I. Petrov, *God. Sofii. Univ. Khim. Fak.*, **63**, 115(1968–69); through *Chem. Abstr.*, **76**, 131822m(1972).

(1022) V. A. Pchelin, *Dokl. Akad. Nauk SSSR*, **204**, 637(1972); through *Chem. Abstr.*, **77**, 105877j(1972).

(1023) J. Sasaki, K. Tajima, and T. Sasaki, *Bull. Chem. Soc. Jap.*, **45**, 348(1972); through *Chem. Abstr.*, **76**, 155950c(1972).

(1024) R. Vochten and G. Petre, *Eur. Biophys. Congr. Proc. 1st*, **4**, 417(1971); through *Chem. Abstr.*, **76**, 76876e(1972).

(1025) J. L. Varsano, *Diss. Abstr., Int. B*, **32**, 7140(1972).

(1026) N. A. Armstrong, *Amer. Cosmet. Perfum.*, **87**, 45(1972).

(1027) B. I. Genkina, I. I. Kravchenko, and M. N. Nasretdinov, *Tr. Bashkir. Nauch.-Issled. Proekt. Inst. Neft. Prom.*, **1970**, 74; through *Chem. Abstr.*, **77**, 154268v(1972).
(1028) V. Y. Tretinnik, V. V. Parkhomenko, N. F. Lozovskaya, A. S. Novotorov, and S. V. Remez, *Fiz.-Khim. Mehk. Liofil'nost Dispersnykh Sist.*, **1971**, 129; through *Chem. Abstr.*, **77**, 156755a (1972).
(1029) N. Veiderpass, L. Kirs, E. Kask, E. Kikkas, T. Saar, and E. Vomm, *Tartu Riikliku Ulikooli Toim.*, **1971**, 92; through *Chem. Abstr.*, **76**, 37379a(1972).
(1030) H. Kimizuka, L. G. Abood, T. Tahara, and K. Kaibara, *J. Colloid Interface Sci.*, **40**, 27(1972); through *Chem. Abstr.*, **77**, 90397b(1972).
(1031) A. A. Abramzon, V. V. Begletsov, V. M. Knat'ko, and E. E. Malakhova, *Kolloid Zh.*, **34**, 155(1972); through *Chem. Abstr.*, **77**, 79780a(1972).
(1032) M. J. Groves, R. M. A. Mustafa, and J. E. Carless, *J. Pharm. Pharmacol.*, **24**, 104P(1972).
(1033) A. I. Rusanov and V. V. Krotov, *Vestn. Leningrad. Univ., Fiz., Khim.*, **1971**, 104; through *Chem. Abstr.*, **76**, 28095c(1972).
(1034) E. H. Lucassen-Reynders, *Kolloid.-Z. Z. Polym.*, **250**, 356 (1972); through *Chem. Abstr.*, **77**, 79796k(1972).
(1035) V. A. Volkov, *Kolloid Zh.*, **33**, 657(1971); through *Chem. Abstr.*, **76**, 47612k(1972).
(1036) H. R. Laesser and H. G. Elias, *Kolloid-Z. Z. Polym.*, **250**, 46(1972); through *Chem. Abstr.*, **77**, 36771f(1972).
(1037) *Ibid.*, **250**, 58(1972); through *Chem. Abstr.*, **77**, 36772g (1972).
(1038) J. G. Watterson, H. R. Laesser, and H. G. Elias, *Kolloid-Z. Z. Polym.*, **250**, 64(1972); through *Chem. Abstr.*, **77**, 36773h (1972).
(1039) H. Lange, *Chem.-Ztg.*, **96**, 192(1972); through *Chem. Abstr.*, **77**, 36765g(1972).
(1040) K. Kralova, M. Nagy, and E. Wolfram, *Magy. Kem. Foly.*, **77**, 436(1971); through *Chem. Abstr.*, **76**, 26656n(1972).
(1041) I. J. Lin, *J. Phys. Chem.*, **76**, 2019(1972); through *Chem. Abstr.*, **77**, 103626c(1972).
(1042) I. J. Lin, *Isr. J. Technol.*, **10**, 195(1972); through *Chem. Abstr.*, **77**, 90383u(1972).
(1043) G. Ben-Et and D. Tatarsky, *J. Amer. Oil Chem. Soc.*, **49**, 499(1972); through *Chem. Abstr.*, **77**, 154279z(1972).
(1044) P. M. Kruglyakov and A. F. Koretskii, *Izv. Sib. Otd. Adad. Nauk SSSR, Ser. Khim. Nauk*, **1971**, 11; through *Chem. Abstr.*, **77**, 36766h(1972).
(1045) H. J. Flath and R. Poeschmann, *Deut. Textiltech.*, **21**, 516 (1971); through *Chem. Abstr.*, **76**, 35444u(1972).
(1046) K. Konno, *Sekiyu Gakkai Shi*, **15**, 271(1972); through *Chem. Abstr.*, **77**, 50527n(1972).
(1047) *Ibid.*, **15**, 363(1972); through *Chem. Abstr.*, **77**, 103625b (1972).
(1048) S. Kucharski, *Wiad. Chem.*, **25**, 641(1971); through *Chem. Abstr.*, **76**, 87519s(1972).
(1049) I. M. Pertsev, G. S. Bashura, I. A. Murav'ev, and E. V. Labunskii, *Farm. Zh. (Kiev)*, **27**, 5(1972); through *Chem. Abstr.*, **77**, 39082t(1972).
(1050) T. Ginsberg, *Treatise Coatings*, **1**, 401(1972); through *Chem. Abstr.*, **76**, 155935b(1972).
(1051) L. Favretto, *Univ. Studi Trieste, Fac. Econ. Commer., Ist. Merceol.* [*Pubbl.*], No. 45(1970); through *Chem. Abstr.*, **76**, 35440q(1972).
(1052) R. Heusch, *Informationsdienst Arbeitsgemeinsch. Pharm. Verfahrenstech.*, **18**, 1(1972); through *Chem. Abstr.*, **77**, 77048u (1972).
(1053) H. Kishimoto, *Nagoya Shiritsu Daigaku Yakugakubu Kenkyu Nempo*, **1970**, 1; through *Chem. Abstr.*, **76**, 5145e(1972).
(1054) M. Katsumi, *Sen'i To Kogyo*, **4**, 451(1971); through *Chem. Abstr.*, **76**, 115186b(1972).
(1055) M. J. Rosen, *J. Amer. Oil Chem. Soc.*, **49**, 293(1972); through *Chem. Abstr.*, **77**, 77044q(1972).
(1056) M. Vanlerberghe, *Rev. Fr. Corps Gras*, **19**, 215(1972); through *Chem. Abstr.*, **77**, 39493c(1972).
(1057) L. S. C. Wan and P. K. C. Poon, *Can. J. Pharm. Sci.*, **6**, 89(1971); through *Chem. Abstr.*, **76**, 101539g(1972).
(1058) R. Huettenrauch and E. Schupp, *Pharmazie*, **27**, 468 (1972); through *Chem. Abstr.*, **77**, 143771c(1972).
(1059) D. G. Hall, *J. Chem. Soc., Faraday Trans. 2*, **68**, 668 (1972); through *Chem. Abstr.*, **76**, 145528g(1972).
(1060) P. Mukerjee, *J. Phys. Chem.*, **76**, 565(1972).
(1061) P. J. Sams, E. Wyn-Jones, and J. Rassing, *Chem. Phys. Lett.*, **13**, 233(1972); through *Chem. Abstr.*, **77**, 21966z(1972).
(1062) J. G. Watterson and H. G. Elias, *Kolloid-Z. Z. Polym.*, **249**, 1136(1971); through *Chem. Abstr.*, **77**, 21958y(1972).
(1063) I. D. Robb, *J. Colloid Interface Sci.*, **37**, 521(1971); through *Chem. Abstr.*, **76**, 61268j(1972).
(1064) N. Muller, *J. Phys. Chem.*, **76**, 3017(1972); through *Chem. Abstr.*, **77**, 156673x(1972).
(1065) S. H. Yalkowsky and G. Zografi, *J. Pharm. Sci.*, **61**, 793 (1972).
(1066) G. Zografi and S. H. Yalkowsky, *ibid.*, **61**, 651(1972).
(1067) C. Tanford, *J. Phys. Chem.*, **76**, 3020(1972).
(1068) K. S. Birdi and H. Kyllingsbaek, *J. Pharm. Pharmacol.*, **23**, 900(1971).
(1069) K. L. Mittal, *J. Pharm. Sci.*, **61**, 1334(1972).
(1070) K. Deguchi and K. Meguro, *J. Colloid Interface Sci.*, **38**, 596(1972); through *Chem. Abstr.*, **77**, 7690y(1972).
(1071) J. M. Corkill and T. Walker, *ibid.*, **39**, 621(1972); through *Chem. Abstr.*, **77**, 77062u(1972).
(1072) J. E. Adderson and C. G. Butler, *J. Pharm. Pharmacol.*, **24**, 130(1972).
(1073) D. Attwood, *ibid.*, **24**, 752(1972).
(1074) M. N. Jones and J. Piercy, *J. Chem. Soc., Faraday Trans. 1*, **68**, 1839(1972); through *Chem. Abstr.*, **77**, 118596s(1972).
(1075) K. Negoro, *Sen'i Kako*, **23**, 313(1971); through *Chem. Abstr.*, **76**, 101531y(1972).
(1076) *Ibid.*, **23**, 474(1971); through *Chem. Abstr.*, **77**, 141704j (1972).
(1077) K. Negoro, *Kami Pa Gikyoshi*, **25**, 459(1971); through *Chem. Abstr.*, **76**, 6947e(1972).
(1078) N. H. Choulis and L. H. Loh, *Can. J. Pharm. Sci.*, **6**, 93 (1971); through *Chem. Abstr.*, **76**, 101540a(1972).
(1079) V. I. Kofanov and Y. M. Glazman, *Ukr. Khim. Zh.*, **38**, 729(1972); through *Chem. Abstr.*, **77**, 116366t(1972).
(1080) H. Florstedt, M. Bornschein, and R. Voight, *Pharmazie*, **26**, 779(1971); through *Chem. Abstr.*, **76**, 76398a(1972).
(1081) E. E. Zaev, *Kolloid Zh.*, **34**, 304(1972); through *Chem. Abstr.*, **76**, 158714q(1972).
(1082) R. C. Dorrance and T. F. Hunter, *J. Chem. Soc. Faraday Trans. 1*, **68**, 1312(1972); through *Chem. Abstr.*, **77**, 52689r(1972).
(1083) M. Miura and M. Kodama, *Bull. Chem. Soc. Jap.*, **45**, 428(1972); through *Chem. Abstr.*, **76**, 155948h(1972).
(1084) N. Shinozuka, H. Suzuki, and S. Hayano, *Kolloid-Z. Z. Polym.*, **248**, 959(1971); through *Chem. Abstr.*, **76**, 115193b(1972).
(1085) M. Han and C. Lee, *Daehan Hwahak Hwoejee*, **16**, 201 (1972); through *Chem. Abstr.*, **77**, 156681y(1972).
(1086) I. Mandru, *Rev. Roum. Chim.*, **16**, 1377(1971); through *Chem. Abstr.*, **76**, 26649n(1972).
(1087) H. Uehara, M. Manabe, and R. Matuura, *Mem. Fac. Sci., Kyushu Univ., Ser. C*, **8**, 55(1972); through *Chem. Abstr.*, **77**, 7689e(1972).
(1088) P. A. Demchenko and N. A. Yaroshenko, *Kolloid Zh.*, **34**, 612(1972); through *Chem. Abstr.*, **77**, 131083s(1972).
(1089) D. F. Bernstein, *Diss. Abstr., Int. B*, **32**, 6317(1972).
(1090) D. F. Bernstein, W. I. Higuchi, and N. F. H. Ho, *J. Colloid Interface Sci.*, **39**, 439(1972); through *Chem. Abstr.*, **77**, 9900r(1972).
(1091) A. G. Sutugin, *Dokl. Akad. Nauk SSSR*, **201**, 647(1971); through *Chem. Abstr.*, **76**, 158739b(1972).
(1092) T. Mitsui, S. Nakamura, F. Harusawa, and Y. Machida, *Kolloid-Z. Z. Polym.*, **250**, 227(1972); through *Chem. Abstr.*, **77**, 128474q(1972).
(1093) G. V. Jeffreys and G. A. Davies, *Recent Advan. Liquid-Liquid Extr.*, **1971**, 495; through *Chem. Abstr.*, **76**, 158677e(1972).
(1094) P. M. Kruglyakov and A. F. Koretskii, *Izv. Sib. Otd. Akad. Nauk SSSR, Ser. Khim. Nauk*, **1971**, 16; through *Chem. Abstr.*, **77**, 52686n(1972).
(1095) A. F. Koretskii and P. M. Kruglyakov, *ibid.*, **1971**, 139; through *Chem. Abstr.*, **76**, 63838u(1972).
(1096) R. D. Vold and K. L. Mittal, *J. Colloid Interface Sci.*, **38**, 451(1972); through *Chem. Abstr.*, **76**, 129197t(1972).
(1097) J. S. Marland and B. A. Mulley, *J. Pharm. Pharmacol.*, **24**, 729(1972).
(1098) R. D. Vold and K. L. Mittal, *J. Pharm. Sci.*, **61**, 769 (1972).
(1099) A. Parera and J. M. Sune, *Ars Pharm.*, **12**, 3(1971);

through *Chem. Abstr.*, **76,** 117457q(1972).
(1100) G. M. Virskaya and K. S. Akhmedov, *Nauch. Tr. Tashkent. Gos. Univ.*, No. 399, **1970,** 208; through *Chem. Abstr.*, **77,** 169083e(1972).
(1101) M. Nakagaki and H. Sunada, *Yakugaku Zasshi*, **92,** 59 (1972).
(1102) W. D. Cooper, *Kolloid-Z. Z. Polym.*, **250,** 38(1972); through *Chem. Abstr.*, **76,** 145269y(1972).
(1103) C. Wang, *J. Clin. Inst. Chem. Eng.*, **2,** 101(1971); through *Chem. Abstr.*, **77,** 39510f(1972).
(1104) J. T. Carstensen, K. P. Stremming, and P. Pothisiri, *J. Pharm. Sci.*, **61,** 1999(1972).
(1105) N. N. Kruglitskii, V. Y. Tretinnik, I. D. Kiseleva, O. L. Alekseev, and V. V. Malyarenko, *Ukr. Khim. Zh. (Russ. Ed.)*, **38,** 456(1972); through *Chem. Abstr.*, **77,** 169166j(1972).
(1106) S. Friberg and K. Roberts, *Nature (London)*, *Phys. Sci.*, **238,** 77(1972); through *Chem. Abstr.*, **77,** 105869h(1972).
(1107) J. Bontoux, A. Rambaud, and B. Reboul, *Trav. Soc. Pharm. Montpellier*, **32,** 51(1972); through *Chem. Abstr.*, **77,** 39122f (1972).
(1108) E. Matijevie, *J. Amer. Oil Chem. Soc.*, **48,** 582(1971); through *Chem. Abstr.*, **76,** 50353g(1972).
(1109) J. T. G. Overbeek, *Chem. Brit.*, **8,** 370(1972); through *Chem. Abstr.*, **77,** 105809p(1972).
(1110) G. A. Martynov and V. M. Muller, *Poverkh. Sily Tonkikh Plenkakh Dispersnykh Sist., Sb. Dokl. Konf. Poverkh. Silam, 4th,* **1969,** 7; through *Chem. Abstr.*, **77,** 169071z(1972).
(1111) J. C. Melrose, *Hydrophobic Surfaces, Kendall Award Symp.*, **5,** 61(1968); through *Chem. Abstr.*, **76,** 76801b(1972).
(1112) A. Kitahara, *Senryo To Yakuhin*, **17,** 191(1972); through *Chem. Abstr.*, **77,** 105810g(1972).
(1113) R. J. Akers, *Amer. Lab.*, **4,** 41(1972); through *Chem. Abstr.*, **77,** 105815n(1972).
(1114) W. U. Malik and A. K. Bhattacharya, *Indian J. Chem.*, **9,** 1002(1971); through *Chem. Abstr.*, **76,** 37752s(1972).
(1115) G. Y. Prilutskii and L. V. Volkov, *Zh. Prikl. Khim. (Leningrad)*, **45,** 212(1972); through *Chem. Abstr.*, **76,** 104212f(1972).
(1116) K. D. Jain and M. K. Sharma, *J. Indian Chem. Soc.*, **48,** 779(1971); through *Chem. Abstr.*, **76,** 74072r(1972).
(1117) J. R. Allegra and S. A. Hawley, *J. Acoust. Soc. Amer.*, **51,** 1545(1972); through *Chem. Abstr.*, **77,** 25238m(1972).
(1118) V. N. Shilov, *Kolloid Zh.*, **34,** 147(1972); through *Chem. Abstr.*, **76,** 90517v(1972).
(1119) K. Aso, S. Mori, and T. Hara, *Kyushu Daigaku Kogaku Shuho*, **45,** 215(1972); through *Chem. Abstr.*, **77,** 105884j(1972).
(1120) R. Lemlich, *J. Soc. Cosmet. Chem.*, **23,** 299(1972).
(1121) I. M. Solomentseva, A. A. Baran, and O. D. Kurilenko, *Dopov. Akad. Nauk Ukr. RSR, Ser. B*, **33,** 1108(1971); through *Chem. Abstr.*, **76,** 101545f(1972).
(1122) J. A. Kitchener, *Brit. Polym. J.*, **4,** 217(1972); through *Chem. Abstr.*, **77,** 116359t(1972).
(1123) O. Petreus and M. Dima, *Stud. Cercet. Chim.*, **20,** 633 (1972); through *Chem. Abstr.*, **77,** 116358s(1972).
(1124) B. W. Barry and G. M. Saunders, *J. Colloid Interface Sci.*, **38,** 616(1972); through *Chem. Abstr.*, **77,** 7669y(1972).
(1125) *Ibid.*, **38,** 626(1972); through *Chem. Abstr.*, **77,** 7670s (1972).
(1126) J. M. P. Papenhuijzen, *Rheol. Acta*, **11,** 73(1972); through *Chem. Abstr.*, **77,** 118592n(1972).
(1127) R. S. Prasad and V. S. Rao, *Indian J. Pharm.*, **34,** 83 (1972); through *Chem. Abstr.*, **77,** 130545g(1972).
(1128) Z. Krowczynsky and B. Kluczykowska, *Proc. Conf. Appl. Phys. Chem., 2nd,* **2,** 711(1971); through *Chem. Abstr.*, **76,** 90012b(1972).
(1129) I. Eros and G. Kedvessy, *ibid.*, **2,** 719(1971); through *Chem. Abstr.*, **76,** 90014d(1972).
(1130) J. E. Carless and J. Ocran, *J. Pharm. Pharmacol.*, **24,** 637(1972).
(1131) L. S. C. Wan, *J. Pharm. Sci.*, **61,** 642(1972).
(1132) O. E. Araujo, *ibid.*, **61,** 1848(1972).
(1133) J. Wozniak, H. Beltman, and W. Pilnik, *Lebensm.-Wiss. Technol.*, **5,** 17(1972); through *Chem. Abstr.*, **76,** 131880d(1972).
(1134) J. D. Topham, *J. Pharm. Sci.*, **61,** 783(1972).
(1135) Z. P. Shul'man, Y. F. Deinega, R. G. Gorodkin, and A. D. Matsepuro, *Progr. Heat Mass Transfer*, **4,** 109(1971); through *Chem. Abstr.*, **76,** 145199a(1972).
(1136) M. Joly, *Surface Colloid Sci.*, **5,** 1(1972); through *Chem. Abstr.*, **77,** 93127z(1972).
(1137) *Ibid.*, **5,** 79(1972); through *Chem. Abstr.*, **77,** 93128a(1972).
(1138) E. E. Finney, Jr., *Food Technol.*, **26**(2), 68(1972).
(1139) L. Adam, Z. Csath Stincel, and V. Ardeleanu, *Rev. Med. (Tirgu-Mures)*, **17,** 422(1971); through *Chem. Abstr.*, **77,** 9568p (1972).
(1140) L. E. Bobrova, V. N. Izmailova, and P. A. Rebinder, *Kolloid Zh.*, **34,** 6(1972); through *Chem. Abstr.*, **76,** 90512q(1972).
(1141) D. T. Wasan, L. Gupta, and M. K. Vora, *AIChE J.*, **17,** 1287(1971); through *Chem. Abstr.*, **76,** 50372n(1972).
(1142) K. Park and T. Ree, *Daehan Hwahak Hwoejee*, **15,** 293 (1971); through *Chem. Abstr.*, **76,** 142876h(1972).
(1143) M. Moo-Young, J. J. Vocadlo, and M. E. Charles, *Can. J. Chem. Eng.*, **50,** 544(1972); through *Chem. Abstr*, **77,** 154289c (1972).
(1144) I. Eros and E. Hunyadvari, *Sci. Pharm.*, **40,** 28(1972); through *Chem. Abstr.*, **76,** 158292a(1972).
(1145) A. Rutkowski and Z. Elsner, *Fette, Seifen Anstrichm.*, **73,** 692(1971); through *Chem. Abstr.*, **76,** 117482u(1972).
(1146) E. F. Panarin, M. V. Solovskii, and N. T. Polyakova, *Fiziol. Opt. Aktiv. Polim. Veshchestva*, **1971,** 181; through *Chem. Abstr.*, **77,** 83453p(1972).
(1147) V. A. Vainshtein and G. N. Naumchik, *Antibiotiki (Moscow)*, **17,** 750(1972); through *Chem. Abstr.*, **77,** 118147w(1972).
(1148) G. Kemp, K. A. Jacobson, and C. E. Wenner, *Biochim. Biophys. Acta*, **255,** 493(1972); through *Chem. Abstr.*, **76,** 148787b (1972).
(1149) L. Biro, M. Arr, and E. Ivan, *Z. Gesamte Inn. Med. Ihre Grenzgeb.*, **27,** 146(1972); through *Chem. Abstr.*, **77,** 43245r(1972).
(1150) S. M. Heman-Ackah and E. R. Garrett, *J. Pharm. Sci.*, **61,** 545(1972).
(1151) K. Seeger and G. Hentschel, *Arzneim.-Forsch.*, **21,** 1590 (1971); through *Chem. Abstr.*, **76,** 68114q(1972).
(1152) N. Rosdahl and V. F. Thomsen, *Ugeskr. Laeger*, **133,** 1817 (1971); through *Chem. Abstr.*, **76,** 68088j(1972).
(1153) B. Kluczykowska and R. Przepiorkowski, *Klin. Oczna*, **41,** 873(1971); through *Chem. Abstr.*, **76,** 117486y(1972).
(1154) Society's Hospital Practice Subcommittee, *Pharm. J.*, **208,** 507(1972).
(1155) J. P. Miller, *Int. Encyl. Pharmacol. Ther.*, **78,** 883(1971); through *Chem. Abstr.*, **76,** 135399b(1972).
(1156) D. E. Van Orden, *J. Lab. Clin. Med.*, **80,** 470(1972).
(1157) S. Y. Chowdhary and A. Jasz, *Radiochem. Radioanal. Lett.*, **8,** 225(1971); through *Chem. Abstr.*, **76,** 37422j(1972).
(1158) K. G. K. Sastry, A. R. Reddy, and A. Nagaratnam, *Proc. Nat. Symp. Radiat. Phys.*, **1970,** 427; through *Chem. Abstr.*, **77,** 52296k(1972).
(1159) S. Ross, *Antimicrob. Ther.*, **1970,** 134; through *Chem. Abstr.*, **76,** 30464r(1972).
(1160) E. Jawetz, *ibid.*, **1970,** 91; through *Chem. Abstr.*, **77,** 30462p(1972).
(1161) H. Bojarska-Dahlig and W. Slawinski, *Wiad. Chem.*, **26,** 81(1972); through *Chem. Abstr.*, **76,** 144761r(1972).
(1162) J. H. C. Nayler, *Proc. Roy. Soc., Ser. B*, **179,** 357(1971); through *Chem. Abstr.*, **76,** 94383w(1972).
(1163) H. Andersgaard, *Norg. Apotekerforen. Tidsskr.*, **80,** 51 (1972); through *Chem. Abstr.*, **77,** 9546e(1972).
(1164) F. E. Hahn, *Antibiot. Chemother. (Basel)*, **17,** 29(1971); through *Chem. Abstr.*, **76,** 67991m(1972).
(1165) A. I. Laskin and J. A. Last, *ibid.*, **17,** 1(1971); through *Chem. Abstr.*, **76,** 67990k(1972).
(1166) G. I. Grishin, *Tr. Leningrad. Khim.-Farm. Inst.*, **27,** 108 (1969); through *Chem. Abstr.*, **76,** 89986r(1972).
(1167) S. Velea and S. Tamasdan, *Farmacia (Bucharest)*, **19,** 705 (1971); through *Chem. Abstr.*, **76,** 89969n(1972).
(1168) S. Velea, *ibid.*, **20,** 129(1972); through *Chem. Abstr.*, **77,** 52239u(1972).
(1169) J. H. Muller, *Int. Encyl. Pharmacol. Ther.*, **78,** 845(1971); through *Chem. Abstr.*, **76,** 135398a(1972).
(1170) L. Von Erichsen, *Deut. Apoth.-Ztg.*, **112,** 484(1972); through *Chem. Abstr.*, **77,** 9543b(1972).
(1171) R. M. Lambrecht, C. Mantescu, C. Redvanly, and A. P. Wolf, *J. Nucl. Med.*, **13,** 266(1972); through *Chem. Abstr.*, **77,** 9575p(1972).
(1172) L. F. Prescott and J. Nimmo, *Acta Pharmacol. Toxicol., Suppl.*, **29,** 288(1971); through *Chem. Abstr.*, **76,** 121399q(1972).
(1173) A. T. Florence, *Pharm. J.*, **208,** 458(1972).

(1174) Pharmaceutical Society's Dept. Pharm. Sci., *ibid.*, **209,** 438(1972).

(1175) R. D. Hossie, I. J. McGilveray, and G. L. Mattok, *Can. Pharm. J.*, **106** (June 1972).

(1176) R. N. Smith, *Lancet*, **2,** 528(1972).

(1177) D. E. Wurster, *J. Mond. Pharm.*, **15,** 21(1972); through *Chem. Abstr.*, **77,** 168514j(1972).

(1178) K. H. Froemming, *Pharm. Ztg.*, **116,** 1474(1971); through *Chem. Abstr.*, **76,** 27890w(1972).

(1179) R. G. Lawrie, *East. Pharm.*, **15,** 15(1972); through *Chem. Abstr.*, **77,** 143753y(1972).

(1180) P. Speiser, *Pharma Int., Engl. Ed.*, **1971,** 5; through *Chem. Abstr.*, **76,** 37358t(1972).

(1181) S. S. Davis, *Brit. Med. J.*, **1,** 102(1972); through *Chem. Abstr.*, **76,** 89972h(1972).

(1182) L. Lachman and W. C. Roemer, *J. Amer. Pharm. Ass.*, **NS12,** 215(1972).

(1183) R. G. Stehle and W. I. Higuchi, *J. Pharm. Sci.*, **61,** 1922 (1972).

(1184) *Ibid.*, **61,** 1931(1972).

(1185) M. A. Augustine and J. Swarbrick, *J. Pharm. Sci.*, **61,** 1656 (1972).

(1186) N. F. H. Ho, J. Turi, C. Shipman, Jr., and W. I. Higuchi, *J. Theor. Biol.*, **34,** 451(1972); through *Chem. Abstr.*, **77,** 13818n (1972).

(1187) J. S. Turi, W. I. Higuchi, C. Shipman, Jr., and N. F. H. Ho, *J. Pharm. Sci.*, **61,** 1618(1972).

(1188) N. F. H. Ho, W. I. Higuchi, and J. S. Turi, *ibid.*, **61,** 192 (1972).

(1189) K. R. M. Vora, W. I. Higuchi, and N. F. H. Ho, *ibid.*, **61,** 1785(1972).

(1190) T. Yotsuyanagi and W. I. Higuchi, *J. Pharm. Pharmacol.*, **24,** 934(1972).

(1191) B. J. Poulsen, *Advan. Biol. Skin*, **12,** 495(1972); through *Chem. Abstr.*, **77,** 109216r(1972).

(1192) M. Katz and B. J. Poulsen, *J. Soc. Cosmet. Chem.*, **23,** 565(1972).

(1193) R. B. Stoughton, *Advan. Biol. Skin*, **12,** 535(1972); through *Chem. Abstr.*, **77,** 109217s(1972).

(1194) C. F. Vickers, *ibid.*, **12,** 177(1972); through *Chem. Abstr.*, **77,** 109211k(1972).

(1195) N. A. Puttnam, *J. Soc. Cosmet. Chem.*, **23,** 209(1972).

(1196) P. Grasso and A. B. G. Lansdown, *ibid.*, **23,** 481(1972).

(1197) V. F. Smolen, B. D. Turrie, and W. A. Weigand, *J. Pharm. Sci.*, **61,** 1941(1972).

(1198) V. F. Smolen, R. G. Barile, and T. G. Theophanous, *ibid.*, **61,** 467(1972).

(1199) E. B. Kirsten and S. M. Ross, *ibid.*, **61,** 1468(1972).

(1200) G. E. Mawer, S. B. Lucas, B. R. Knowles, and R. M. Stirland, *Lancet*, **1,** 12(1972).

(1201) R. W. Jeliffe, *J. Mond. Pharm.*, **15,** 53(1972); through *Chem. Abstr.*, **77,** 83329c(1972).

(1202) K. H. Froemming, B. Lippold, and E. R. Garrett, *Mitt. Deut. Pharm. Ges.*, **41,** 205(1971); through *Chem. Abstr.*, **76,** 27889c (1972).

(1203) H. Roepke and J. Riemann, *Advan. Biosci.*, **5,** 55(1970); through *Chem. Abstr.*, **76,** 121378g(1972).

(1204) G. Giorgi and G. Segre, *ibid.*, **5,** 89(1970); through *Chem. Abstr.*, **76,** 121379h(1972).

(1205) H. M. Von Hattingberg, *Arzneim.-Forsch.*, **22,** 305(1972); through *Chem. Abstr.*, **77,** 121948p(1972).

(1206) G. E. Schumacher, *Amer. J. Hosp. Pharm.*, **29,** 474(1972).

(1207) J. G. Wagner, *Med. Chem., Ser. Monogr.*, **11,** 451(1971); through *Chem. Abstr.*, **76,** 131403a(1972).

(1208) J. B. Mielck and P. P. Speiser, *Pharmazie*, **26,** 652(1971); through *Chem. Abstr.*, **76,** 94368v(1972).

(1209) E. R. Garrett, *Acta Pharmacol. Toxicol., Suppl.*, **29,** 1 (1971); through *Chem. Abstr.*, **76,** 89970f(1972).

(1210) L. Krowczynski, *Farm. Pol.*, **28,** 469(1972); through *Chem. Abstr.*, **77,** 96655f(1972).

(1211) C. A. Byrle, *Rev. Farm. (Buenos Aires)*, **114,** 13(1972); through *Chem. Abstr.*, **77,** 105533u(1972).

(1212) W. J. Westlake, *J. Pharm. Sci.*, **61,** 1340(1972).

(1213) R. Bastide, R. Rouffiac, and E. Stanislas, *Pharm. Acta Helv.*, **47,** 295(1972); through *Chem. Abstr.*, **77,** 92816m(1972).

(1214) K. Kubota, *Hyomen*, **8,** 773(1972); through *Chem. Abstr.*, **77,** 96695u(1972).

(1215) T. Teorell, *Advan. Biosci.*, **5,** 21(1969); through *Chem. Abstr.*, **76,** 121377f(1972).

(1216) N. G. M. Bishara, *Gyogyszereszet*, **15,** 411(1971); through *Chem. Abstr.*, **76,** 131400x(1972).

(1217) H. Barry, III, F. Marcus, and J. L. Colaizzi, *J. Pharm. Sci.*, **61,** 172(1972).

(1218) H. Pratzel, *Arzneim.-Forsch.*, **22,** 585(1972); through *Chem. Abstr.*, **77,** 83358m(1972).

(1219) P. Hebborn, *Advan. Biol. Skin*, **12,** 111(1972); through *Chem. Abstr.*, **77,** 109210j(1972).

(1220) A. Rey, *Labo-Pharma-Probl. Tech.*, **19,** 48(1971); through *Chem. Abstr.*, **76,** 94381u(1972).

(1221) B. Belleau, *Advan. Chem. Ser.*, **108,** 141(1971); through *Chem. Abstr.*, **76,** 94372s(1972).

(1222) G. Levy, *Acta Pharmacol. Toxicol., Suppl.*, **29,** 203(1971); through *Chem. Abstr.*, **76,** 121394j(1972).

(1223) I. Taddei, *Riv. Ital. Essenze Profumi Piante Offic. Aromi Saponi Cosmet. Aerosol*, **53,** 658(1971); through *Chem. Abstr.*, **76,** 131356n(1972).

(1224) R. D. Hossiet, I. J. McGilveray, and G. L. Mattok, *Can. Pharm. J.*, **261,** 188(1972).

(1225) W. L. Chiou, *J. Pharm. Pharmacol.*, **24,** 342(1972).

(1226) G. Graham and M. Rowland, *J. Pharm. Sci.*, **61,** 1219 (1972).

(1227) J. D. Gabourel, *Advan. Biol. Skin*, **12,** 51(1972); through *Chem. Abstr.*, **77,** 109206n(1972).

(1228) V. M. Rosenoer and G. M. Gill, *Med. Clin. N. Amer.*, **56,** 585(1972); through *Chem. Abstr.*, **77,** 56267z(1972).

(1229) M. Rowland, *Advan. Biol. Skin*, **12,** 235(1972); through *Chem. Abstr.*, **77,** 109213n(1972).

(1230) L. H. Perrin and J. Fabre, *Schweiz. Apoth.-Ztg.*, **109,** 576 (1971); through *Chem. Abstr.*, **76,** 30478y(1972).

(1231) F. Heim, *Fortschr. Med.*, **89,** 907(1971); through *Chem. Abstr.*, **76,** 30476w(1972).

(1232) E. S. Manley, Jr., and J. Belote, *J. Pharm. Sci.*, **61,** 1401 (1972).

(1233) I. H. Stockley, *Pharm. J.*, **208,** 16(1972); through *Chem. Abstr.* **76,** 148610p(1972).

(1234) W. Luinsky, E. Conrad, and R. Van De Bogart, *Nature*, **239,** 165(1972).

(1235) R. S. Levinson, *Diss. Abstr., Int. B*, **33,** 2177(1972).

(1236) K. Kikugawa and K. Iizuka, *J. Pharm. Sci.*, **61,** 1904 (1972).

(1237) H. Schott and C. Y. Young, *ibid.*, **61,** 182(1972).

(1238) C. H. Morris, J. E. Christian, T. S. Miya, and W. G. Hansen, *ibid.*, **61,** 815(1972).

(1239) G. Steiner, P. Pothisiri, and J. T. Carstensen, *ibid.*, **61,** 2009(1972).

(1240) J. Wenger and M. Sundy, *J. Clin. Pharmacol. New Drugs*, **12,** 136(1972).

(1241) J. K. Seydel, *Med. Chem., Ser. Monogr.*, **11,** 343(1971); through *Chem. Abstr.*, **76,** 121355x(1972).

(1242) E. J. Ariens, *Chimia*, **26,** 355(1972); through *Chem. Abstr.*, **77,** 96665j(1972).

(1243) E. J. Ariens, *Afinidad*, **28,** 1237(1971); through *Chem. Abstr.*, **76,** 158227h(1972).

(1244) C. Hansch and W. J. Dunn, III, *J. Pharm. Sci.*, **61,** 1 (1972).

(1245) M. S. Tute, *Advan. Drug Res.*, **6,** 1(1971); through *Chem. Abstr.*, **76,** 148639e(1972).

(1246) C. M. Bowman, V. B. Bond, N. L. Lee, D. R. Petersen, and M. H. Reslock, *J. Chem. Doc.*, **11,** 168(1971); through *Chem. Abstr.*, **77,** 56422w(1972).

(1247) J. G. Topliss, *J. Med. Chem.*, **15,** 1006(1972).

(1248) S. S. Davis, T. Higuchi, and J. H. Rytting, *J. Pharm. Pharmacol.*, **24,** 30P(1972).

(1249) J. H. Rytting, S. S. Davis, and T. Higuchi, *J. Pharm. Sci.*, **61,** 816(1972).

(1250) A. Cammarata, *J. Med. Chem.*, **15,** 573(1972).

(1251) J. G. Topliss and R. J. Costello, *ibid.*, **15,** 1066(1972).

(1252) P. R. Andrews, *ibid.*, **15,** 1069(1972).

(1253) Y. C. Martin, P. H. Jones, T. J. Perun, W. E. Grundy, S. Bell, R. R. Bower, and N. L. Shipkowitz, *ibid.*, **15,** 635(1972).

(1254) A. M. Barbaro, M. C. Guerra, and G. L. Biagi, *Boll. Soc. Ital. Biol. Sper.*, **47,** 556(1971); through *Chem. Abstr.*, **76,** 149482k (1972).

(1255) J. H. C. Nayler, *Antibiotiki (Moscow)*, **16,** 877(1971);

through *Chem. Abstr.*, **76**, 30451j(1972).
(1256) A. E. Bird and J. H. C. Nayler, *Med. Chem., Ser. Monogr.*, **11**, 277(1971); through *Chem. Abstr.*, **77**, 37g(1972).
(1257) R. Bourdon, *Boll. Soc. Ital. Farm. Osp.*, **17**, 261(1971); through *Chem. Abstr.*, **76**, 148635a(1972).
(1258) J. C. Dearden and E. Tomlinson, *J. Pharm. Pharmacol.*, **24**, 115P(1972).
(1259) W. R. Glave and C. Hansch, *J. Pharm. Sci.*, **61**, 589(1972).
(1260) P. N. Craig, *J. Med. Chem.*, **15**, 144(1972).
(1261) K. J. Chang, R. C. Deth, and D. J. Triggle, *ibid.*, **15**, 243 (1972).
(1262) M. Frisk-Homlberg and E. Van der Kleijn, *Eur. J. Pharmacol.*, **18**, 139(1972); through *Chem. Abstr.*, **77**, 56395q (1972).
(1263) R. T. Buckler, *J. Med. Chem.*, **15**, 578(1972).
(1264) M. D. Guerra, A. M. Barbaro, and G. L. Biagi, *Boll. Soc. Ital. Biol. Sper.*, **47**, 553(1971); through *Chem. Abstr.*, **76**, 148736j(1972).
(1265) I. W. Mathison, P. H. Morgan, R. R. Tidwell, and C. R. Handorf, *J. Pharm. Sci.*, **61**, 637(1972).
(1266) H. P. Buech, *Arzneim.-Forsch.*, **21**, 1493(1971); through *Chem. Abstr.*, **76**, 135546x(1972).
(1267) J. G. Topliss and M. D. Yudis, *J. Med. Chem.*, **15**, 394 (1972).
(1268) *Ibid.*, **15**, 400(1972).
(1269) H. Choi, *Diss. Abstr., Int. B*, **32**, 6940(1972).
(1270) J. M. Clayton, *ibid.*, **32**, 6941(1972).
(1271) C. Hansch and W. R. Glave, *J. Med. Chem.*, **15**, 112 (1972).
(1272) R. A. Wiley, B. A. Faraj, A. Jantz, and M. M. Hava, *ibid.*, **15**, 374(1972).
(1273) B. A. Faraj, *Diss. Abstr., Int. B*, **33**, 2539(1972).
(1274) V. S. Vaidhyanathan, *J. Pharm. Sci.*, **61**, 894(1972).
(1275) *Ibid.*, **61**, 2001(1972).
(1276) W. L. Hayton, *Diss. Abstr., Int. B*, **32**, 5280(1972).
(1277) W. L. Hayton, D. E. Guttman, and G. Levy, *J. Pharm. Sci.*, **61**, 356(1972).
(1278) W. L. Hayton and G. Levy, *ibid.*, **61**, 362(1972).
(1279) *Ibid.*, **61**, 367(1972).
(1280) W. L. Hayton, G. Levy, and C. Regardh, *J. Pharm. Sci.*, **61**, 473(1972).
(1281) W. L. Hayton and G. Levy, *ibid.*, **61**, 649(1972).
(1282) S. Furusawa, K. Okumura, and H. Sezaki, *J. Pharm. Pharmacol.*, **24**, 272(1972).
(1283) A. Felmeister, *J. Pharm. Sci.*, **61**, 151(1972).
(1284) K. Larsson, B. Noren, and G. Odham, *Biochem. Pharmacol.*, **21**, 947(1972).
(1285) D. W. Blois and J. Swarbrick, *J. Pharm. Sci.*, **61**, 390 (1972).
(1286) *Ibid.*, **61**, 393(1972).
(1287) H. Bruns, *Chem.-Ztg.*, **96**, 417(1972); through *Chem. Abstr.*, **77**, 147382z(1972).
(1288) C. Hansch, *Med. Chem., Ser. Monogr.*, **11**, 271(1971); through *Chem. Abstr.*, **76**, 121354w(1972).
(1289) A. Burger, *Fundam. Conc. Drug-Receptor Interactions, Proc. Buffalo-Milan Symp. Mol. Pharmacol., 3rd*, **1968**, 1; through *Chem. Abstr.*, **76**, 80911e(1972).
(1290) G. E. Schumacher, *Amer. J. Hosp. Pharm.*, **29**, 339(1972).
(1291) P. C. Hirom, P. Millburn, and R. L. Smith, *J. Mond. Pharm.*, **15**, 10(1972); through *Chem. Abstr.*, **77**, 83328b(1972).
(1292) E. Mizuta, J. Toda, N. Suzuki, H. Sugibayashi, K. Imai, and M. Nishikawa, *Chem. Pharm. Bull.*, **20**, 1114(1972).
(1293) A. J. Wohl, *Med. Chem., Ser. Monogr.*, **11**, 381(1971); through *Chem. Abstr.*, **76**, 131402z(1972).
(1294) L. B. Kier, *Fundam. Conc. Drug-Receptor Interactions, Proc. Buffalo-Milan Symp. Mol. Pharmacol., 3rd*, **1968**, 15; through *Chem. Abstr.*, **76**, 80912f(1972).
(1295) M. J. Mercier and P. A. Dumont, *J. Pharm. Pharmacol.*, **24**, 706(1972).
(1296) T. M. Bustard and Y. C. Martin, *J. Med. Chem.*, **15**, 1101 (1972).
(1297) H. Hint, *Dextrans, Int. Symp., 1st*, **1968**, 3; through *Chem. Abstr.*, **76**, 94356q(1972).
(1298) H. R. Stoll, H. Nitschmann, K. Aeberhard, and J. R. Guenter, *Bibl. Haematol. (Basel)*, No. 33, 96(1969); through *Chem. Abstr.*, **76**, 41820e(1972).
(1299) E. J. Ariens, *Med. Chem., Ser. Monogr.*, **11**, 1(1971); through *Chem. Abstr.*, **77**, 35e(1972).
(1300) H. Terada, *Hyomen*, **8**, 391(1970); through *Chem. Abstr.*, **77**, 96694t(1972).
(1301) B. C. Lippold, *Pharm. Unserer Zeit*, **1**, 55(1972); through *Chem. Abstr.*, **77**, 79514s(1972).
(1302) C. P. Schaffner and W. Mechlinski, *J. Antibiot.*, **25**, 259 (1972); through *Chem. Abstr.*, **77**, 97014h(1972).
(1303) T. Nambara, K. Shimada, and J. Goto, *Sogo Rinsho*, **21**, 465(1972); through *Chem. Abstr.*, **77**, 56266y(1972).
(1304) R. K. Malhotra, *Pharmacos*, **16**, 21(1971); through *Chem. Abstr.*, **76**, 148632x(1972).
(1305) H. Schoenenberger, A. Petter, and W. Zwez, *Pharmazie*, **27**, 522(1972); through *Chem. Abstr.*, **77**, 159957d(1972).
(1306) R. W. Fuller and M. M. Marsh, *J. Med. Chem.*, **15**, 1068 (1972).
(1307) S. Javidan-Nejad, *Diss. Abstr., Int. B*, **33**, 2176(1972).
(1308) M. Nakagaki, A. Kondo, Y. Kamkjo, Y. Odakura, and M. Suzuki, *Yakugaku Zasshi*, **92**, 1218(1972).
(1309) S. H. Curry, *J. Pharm. Pharmacol.*, **24**, 818(1972).
(1310) G. H. Miller, P. H. Doukas, and J. K. Seydel, *J. Med. Chem.*, **15**, 700(1972).
(1311) R. B. Barlow, F. M. Franks, and J. D. M. Pearson, *J. Pharm. Pharmacol.*, **24**, 753(1972).
(1312) M. Sung and J. A. Parker, *Proc. Nat. Acad. Sci. USA*, **69**, 1346(1972); through *Chem. Abstr.*, **77**, 83397y(1972).
(1313) D. Mikhailova and R. Nacheva, *Farmatsiya (Sofia)*, **21**, 1(1971); through *Chem. Abstr.*, **76**, 131428n(1972).
(1314) C. Radouco-Thomas, F. Garcin, S. Radouco-Thomas, P. Singh, G. Nosal, J. Huot, and T. K. Wang, *Int. Z. Klin. Pharmakol. Ther. Toxikol.*, **5**, 231(1971); through *Chem. Abstr.*, **76**, 148629b (1972).
(1315) A. Jung, H. Luellmann, and A. Ziegler, *Eur. J. Pharmacol.*, **15**, 327(1971); through *Chem. Abstr.*, **76**, 41819m(1972).
(1316) S. A. Khalil, M. A. Moustafa, A. R. Ebian, and M. M. Motawi, *J. Pharm. Sci.*, **61**, 1615(1972).
(1317) E. I. Stupak, *Diss. Abstr., Int. B*, **33**, 2677(1972).
(1318) E. I. Stupak and T. R. Bates, *J. Pharm. Sci.*, **61**, 400(1972).
(1319) C. B. Pratt and M. Verzosa, *Clin. Pharmacol. Ther.*, **13**, 343(1972).
(1320) G. Levy and B. K. Rao, *J. Pharm. Sci.*, **61**, 279(1972).
(1321) Z. Korossyova and L. Zathurecky, *Pharmazie*, **26**, 682 (1971); through *Chem. Abstr.*, **76**, 94653j(1972).
(1322) J. H. Collett and R. Whithington, *J. Pharm. Pharmacol.*, **24**, 211(1972).
(1323) P. Ionescu-Stoian, E. Savopol, and V. Barcari, *Farmacia (Bucharest)*, **19**, 529(1971); through *Chem. Abstr.*, **76**, 76401w (1972).
(1324) P. Ionescu-Stoian, E. Savopol, L. Smal, and V. Barcari, *ibid.*, **19**, 535(1971); through *Chem. Abstr.*, **76**, 76402x(1972).
(1325) P. Ionescu-Stoian, E. Savopol, V. Barcari, and D. Dinca, *ibid.*, **19**, 591(1971); through *Chem. Abstr.*, **76**, 103672u(1972).
(1326) M. J. Akers, *Diss. Abstr., Int. B*, **33**, 1642(1972).
(1327) J. M. Aiache, P. Armoiry, and P. Febvre, *C. R. Soc. Biol.*, **165**, 1310(1971); through *Chem. Abstr.*, **77**, 24805g(1972).
(1328) J. R. Leonards and G. Levy, *Arch. Intern. Med.*, **129**, 457 (1972); through *Chem. Abstr.*, **76**, 158272u(1972).
(1329) J. P. Delporte and F. Jaminet, *Pharm. Acta Helv.*, **47**, 98 (1972); through *Chem. Abstr.*, **77**, 28725d(1972).
(1330) W. H. Barr, L. M. Gerbracht, K. Letcher, M. Plaut, and N. Strahl, *Clin. Pharmacol. Ther.*, **13**, 97(1972).
(1331) B. Katchen, *Acta Pharmacol. Toxicol., Suppl.*, **29**, 88(1971); through *Chem. Abstr.*, **76**, 121939r(1972).
(1332) Y. Langlois, M. A. Gagnon, and L. Tetreault, *J. Clin. Pharmacol. New Drugs*, **12**, 196(1972); through *Chem. Abstr.*, **77**, 43424y(1972).
(1333) K. A. Javaid and C. W. Hartman, *J. Pharm. Sci.*, **61**, 900 (1972).
(1334) G. A. Ellard, P. T. Gammon, S. Lakshiminarayan, W. Fox, V. R. Aber, D. A. Mitchison, K. M. Citron, and R. Tall, *Lancet*, **1**, 340(1972).
(1335) C. J. Benoy, L. A. Elson, and R. Schneider, *Brit. J. Pharmacol.*, **45**, 135p(1972); through *Chem. Abstr.*, **77**, 83564a(1972).
(1336) P. A. Gresham, M. Barnett, S. V. Smith, and R. Schneider, *Nature (London)*, **234**, 149(1971); through *Chem. Abstr.*, **76**, 81273k (1972).
(1337) A. M. Nicaise and J. Pollet, *Therapie*, **27**, 465(1972); through *Chem. Abstr.*, **77**, 96891e(1972).

(1338) H. P. Jaspersen, *Informationsdienst Arbeitsgemeinsch. Pharm. Verfahrenstech.*, **18,** 32(1972); through *Chem. Abstr.*, **77,** 56286e(1972).

(1339) K. H. Burdick, *Acta Dermato.-Venereol., Suppl.*, **52,** 19 (1972); through *Chem. Abstr.*, **77,** 66165d(1972).

(1340) A. F. Pepler, R. Woodford, and J. C. Morrison, *Brit. J. Dermatol.*, **85,** 171(1971); through *Chem. Abstr.*, **76,** 10420v(1972).

(1341) M. Mezei and K. J. Ryan, *J. Pharm. Sci.*, **61,** 1329(1972).

(1342) G. T. W. Chen, *Diss. Abstr., Int. B*, **33,** 2176(1972).

(1343) J. Hadgraft, J. W. Hadgraft, and I. Sarkany, *Brit. J. Dermatol.*, **87,** 36(1972); through *Chem. Abstr.*, **77,** 96997u(1972).

(1344) E. Z. Kagan, V. G. Koroleva, and E. N. Lazareva, *Antibiotiki (Moscow)*, **16,** 987(1971); through *Chem. Abstr.*, **76,** 37387b (1972).

(1345) P. Hlavaty, M. Valentova, J. Augustin, and L. Drobnica, *Acta Fac. Med. Univ. Brun.*, **1972,** 189; through *Chem. Abstr.*, **77,** 109240u(1972).

(1346) A. Mayer and J. Sallay, *Pharmazie*, **26,** 692(1971); through *Chem. Abstr.*, **76,** 94500g(1972).

(1347) K. H. Luedde, *Acta Fac. Med. Univ. Brun.*, **1972,** 311; through *Chem. Abstr.*, **77,** 109394x(1972).

(1348) H. I. Silverman, *Drug Cosmet. Ind.*, **110**(5), 44(1972).

(1349) K. Kakemi, H. Sezaki, K. Okumura, H. Kobayashi, and S. Furusawa, *Chem. Pharm. Bull.*, **20,** 443(1972).

(1350) O. Loew, G. Machnik, G. Simon, and H. Schicketanz, *Zentralbl. Pharm. Pharmakotherapie Laboratoriumsdiagnostik*, **110,** 925(1971); through *Chem. Abstr.*, **76,** 68166h(1972).

(1351) G. Machnik, O. Loew, K. H. Chemnitius, R. Ernst, and R. Wagenknecht, *ibid.*, **110,** 931(1971); through *Chem. Abstr.*, **76,** 68167j(1972).

(1352) J. C. Taggart, *PDA Bull.*, **26,** 87(1972).

(1353) K. Stochla, *Farm. Pol.*, **28,** 497(1972); through *Chem. Abstr.*, **77,** 52236r(1972).

(1354) E. E. Galal, A. H. Gobba, S. Wilson, M. K. Madkour, and A. Kandil, *J. Drug. Res.*, **3,** 171(1971); through *Chem. Abstr.*, **77,** 109258f(1972).

(1355) T. R. D. Shaw, M. R. Howard, and J. Hamer, *Lancet*, **2,** 303(1972).

(1356) A. La Manna, *Farmacista*, **24,** 11(1971); through *Chem. Abstr.*, **76,** 135460q(1972).

(1357) K. Muenzel, *Pharm. Acta Helv.*, **46,** 513(1971); through *Chem. Abstr.*, **76,** 20a(1972).

(1358) R. A. Anderson and W. Sneddon, *Med. J. Aust.*, **1,** 585 (1972); through *Chem. Abstr.*, **77,** 92818p(1972).

(1359) A. W. Czerwinski, K. L. Evensen, M. L. Clark, and T. L. Whitsett, *U. S. Nat. Tech. Inform. Serv., AD Rep.*, No. 731871 (1971); through *Chem. Abstr.*, **76,** 90001x(1972).

(1360) A. Hurwitz, *J. Pharmacol. Exp. Ther.*, **179,** 485(1971); through *Chem. Abstr.*, **76,** 81089e(1972).

(1361) P. Lechat and J. P. Giroud, *Int. Encyl. Pharmacol. Ther.*, **8,** 261(1967); through *Chem. Abstr.*, **76,** 121308j(1972).

(1362) V. J. Stella, *Diss. Abstr., Int. B*, **32,** 5705(1972).

(1363) M. Movrin, *Farm. Glas.*, **27,** 301(1971); through *Chem. Abstr.*, **76,** 158256s(1972).

(1364) R. J. Withey, G. R. VanPetten, and H. F. Lettau, *J. Clin. Pharmacol. New Drugs*, **12,** 190(1972); through *Chem. Abstr.*, **77,** 43423x(1972).

(1365) K. H. Groezinger, A. Volkwein, and R. Boehler, *Arzneim.-Forsch.*, **22,** 1152(1972); through *Chem. Abstr.*, **77,** 168542s(1972).

(1366) H. Turakka, M. M. Airaksinen, and V. E. Krogerus, *Farm. Aikak.*, **81,** 29(1972); through *Chem. Abstr.*, **77,** 56354a (1972).

(1367) O. Folkenborg, *Ugeskr. Laeger*, **134,** 266(1972); through *Chem. Abstr.*, **77,** 56331r(1972).

(1368) D. C. Monkhouse and J. L. Lach, *Can. J. Pharm. Sci.*, **7,** 29(1972).

(1369) F. M. Thompson and L. J. Libertini, *Science*, **178,** 505 (1972).

(1370) H. Kurisu and R. Kawahara, *Eisei Shikenjo Hokoku*, **89,** 143(1971); through *Chem. Abstr.*, **77,** 7692a(1972).

(1371) R. D. Sofia, R. K. Kubena, and H. Barry, III, *J. Pharm. Pharmacol.*, **23,** 889(1971).

(1372) R. M. DeHaan and D. Schellenberg, *J. Clin. Pharmacol. New Drugs*, **12,** 74(1972); through *Chem. Abstr.*, **76,** 135976n (1972).

(1373) R. M. DeHaan, W. D. VandenBosch, and C. M. Metzler, *ibid.*, **12,** 205(1972); through *Chem. Abstr.*, **77,** 43051z(1972).

(1374) R. Jeppsson, *Acta Pharm. Suecica*, **9,** 199(1972); through *Chem. Abstr.*, **77,** 96886g(1972).

(1375) J. Sardal, J. Baillet, and R. Claude, *Therapie*, **27,** 473 (1972); through *Chem. Abstr.*, **77,** 96892f(1972).

(1376) J. E. Winther and M. W. Khan, *Acta Odontol. Scand.*, **29,** 337(1971); through *Chem. Abstr.*, **76,** 81344j(1972).

(1377) A. Bovis and M. Lanza, *Bull. Soc. Pharm. Marseille*, **20,** 55(1971); through *Chem. Abstr.*, **77,** 39104b(1972).

(1378) S. L. Yankell, *Advan. Biol. Skin*, **12,** 511(1972); through *Chem. Abstr.*, **77,** 109236x(1972).

(1379) C. Wollman, F. U. Meyer, and W. Schwenke, *Deut. Gesundheitsw.*, **27,** 1571(1972); through *Chem. Abstr.*, **77,** 160204n (1972).

(1380) K. H. Luedde, *Acta Fac. Med. Univ. Brun.*, **1972,** 183; through *Chem. Abstr.*, **77,** 92781w(1972).

(1381) P. Febvre, J. M. Aiache, P. Jabot, and P. Armoiry, *C. R. Soc. Biol.*, **164,** 1700(1970); through *Chem. Abstr.*, **76,** 6702w(1972).

(1382) L. F. Saraiva de Paiva, L. S. Carvalho, and M. A. Rego, *Rev. Port. Farm.*, **21,** 77(1971); through *Chem. Abstr.*, **76,** 63133k (1972).

(1383) R. Canela, M. C. Sanchez, J. E. Beneyto, F. Vericat, I. Tintore, V. M. Almirall, and J. Colome, *Arch. Inst. Farmacol. Exp., Madrid*, **23,** 65(1971); through *Chem. Abstr.*, **77,** 28721z(1972).

(1384) E. R. Clark and A. M. McCracken, *J. Endocrinol.*, **51,** 797 (1971); through *Chem. Abstr.*, **76,** 6697y(1972).

(1385) G. Gregoriadis and B. E. Ryman, *Biochem. J.*, **124,** 58P (1971); through *Chem. Abstr.*, **76,** 42001a(1972).

(1386) I. M. Pertsev, G. S. Bashura, D. P. Salo, I. A. Murav'ev, and O. A. Pimenov, *Farm. Zh. Kiev*, **27,** 18(1972); through *Chem. Abstr.*, **77,** 105534v(1972).

(1387) T. Tsuchiya and G. Levy, *J. Pharm. Sci.*, **61,** 586(1972).

(1388) T. Tsuchiya, *Diss. Abstr., Int. B*, **33,** 801(1972).

(1389) G. Levy and T. Tsuchiya, *Clin. Pharmacol. Ther.*, **13,** 317 (1972).

(1390) T. Tsuchiya and G. Levy, *J. Pharm. Sci.*, **61,** 624(1972).

(1391) J. Ivan, *Acta Pharm. Hung.*, **42,** 103(1972); through *Chem. Abstr.*, **77,** 43054c(1972).

(1392) K. Muenzel, *Acta Pharmacol. Toxicol., Suppl.*, **29,** 81 (1971); through *Chem. Abstr.*, **76,** 121938q(1972).

(1393) W. H. Johns and T. R. Bates, *J. Pharm. Sci.*, **61,** 730 (1972).

(1394) *Ibid.*, **61,** 735(1972).

(1395) F. B. Thomas, D. Salsburey, and N. J. Greenberger, *Amer. J. Dig. Dis.*, **17,** 263(1972); through *Chem. Abstr.*, **77,** 56622m (1972).

(1396) J. F. Adams, D. J. Clow, S. K. Ross, K. Boddy, P. King, and M. A. Mahaffy, *Clin. Sci.*, **43,** 233(1972); through *Chem. Abstr.*, **77,** 121983w(1972).

(1397) K. Morokuma, *Vitamins*, **44,** 69(1971); through *Chem. Abstr.*, **76,** 94419n(1972).

(1398) K. Terato, T. Fujita, and Y. Yoshino, *Yakugaku Zasshi*, **92,** 1247(1972).

(1399) T. Nadai, K. Nishii, and A. Tatematsu, *ibid.*, **92,** 384 (1972).

(1400) *Ibid.*, **92,** 388(1972).

(1401) H. J. Eyssen, J. F. VandenBosch, G. A. Janssen, and H. Vanderhaeghe, *Atherosclerosis*, **14,** 181(1971); through *Chem. Abstr.*, **76,** 94414g(1972).

(1402) H. Eyssen, H. Vanderhaeghe, and P. De Somer, *Fed. Proc., Fed. Amer. Soc. Exp. Biol.*, **30,** 1803(1971); through *Chem. Abstr.*, **76,** 41792x(1972).

(1403) T. Y. Koh and K. R. Bharucha, *J. Lab. Clin. Med.*, **80,** 47 (1972).

(1404) B. Rizov, D. Dimitrov, A. Aleksieva, and E. Pashova, *Amer. J. Obstet. Gynecol.*, **114,** 103(1972); through *Chem. Abstr.*, **77,** 147757a(1972).

(1405) G. Levy, M. Gibaldi, and J. A. Procknal, *J. Pharm. Sci.*, **61,** 798(1972).

(1406) S. Goto, O. Tsuzuki, and S. Iguchi, *ibid.*, **61,** 945(1972).

(1407) A. Hurwitz and M. B. Sheehan, *J. Pharmacol. Exp. Ther.*, **179,** 124(1971); through *Chem. Abstr.*, **76,** 10376k(1972).

(1408) R. L. Lucarotti, J. L. Colaizzi, H. Barry, III, and R. I. Poust, *J. Pharm. Sci.*, **61,** 903(1972).

(1409) C. D. Gerson, G. W. Hepner, N. Brown, N. Cohen, V. Herbert, and H. D. Janowitz, *Gastroenterology*, **63,** 246(1972); through *Chem. Abstr.*, **77,** 109543v(1972).

(1410) S. H. Sloan, T. H. Pettit, and K. D. Litwack, *Amer. J.*

Ophthalmol., **73**, 750(1972); through *Chem. Abstr.*, **77**, 56670a (1972).
(1411) L. Dettli, P. Spring, and S. Ryter, *Acta Pharmacol. Toxicol. Suppl.*, **29**, 211(1971); through *Chem. Abstr.*, **76**, 121395k(1972).
(1412) I. J. McGilveray and G. L. Mattok, *J. Pharm. Pharmacol.*, **24**, 615(1972).
(1413) M. Pfeffer and J. M. Schor, *J. Pharm. Sci.*, **61**, 1223(1972).
(1414) J. D. Nelson, S. Shelton, H. T. Kusmiexz, and K. C. Haltalin, *Clin. Pharmacol. Ther.*, **13**, 879(1972).
(1415) E. I. Eger, II, S. H. Bahlman, and E. S. Munson, *Anesthesiology*, **35**, 365(1971); through *Chem. Abstr.*, **76**, 30452k(1972).
(1416) H. Pavlovitch, C. Fellot, and S. Balsan, *C. R. Acad. Sci. Ser. D*, **274**, 3152(1972); through *Chem. Abstr.*, **77**, 97001b(1972).
(1417) M. Rowland, *J. Pharm. Sci.*, **61**, 70(1972).
(1418) C. R. Cleaveland and D. G. Shand, *Clin. Pharmacol. Ther.*, **13**, 181(1972).
(1419) T. O. McDonald and A. R. Borgmann, *Ann. Ophthalmol.*, **3**, 1135(1971); through *Chem. Abstr.*, **76**, 30641w(1972).
(1420) *Ibid.*, **3**, 1146(1971); through *Chem. Abstr.*, **76**, 30642x (1972).
(1421) V. S. Pugachev, *Probl. Tuberk.*, **49**, 51(1971); through *Chem. Abstr.*, **76**, 30667j(1972).
(1422) T. J. H. Clark, *Lancet*, **1**, 1361(1972).
(1423) P. L. Kamburoff, S. Bianco, J. P. Griffin, and F. J. Prime, *Bull. Physio-Pathol. Resp.*, **8**, 685(1972); through *Chem. Abstr.*, **77**, 160271g(1972).
(1424) A. H. Beckett and L. G. Brookes, *J. Pharm. Phamacol.*, **23**, 837(1971).
(1425) M. K. Younoszai, H. P. Schedl, M. Young, and E. Anderson, *Proc. Soc. Exp. Biol. Med.*, **140**, 496(1972); through *Chem. Abstr.*, **77**, 43340t(1972).
(1426) E. L. Krawitt and P. A. Stubbert, *ibid.*, **140**, 420(1972); through *Chem. Abstr.*, **77**, 43338y(1972).
(1427) R. M. Taketa, R. N. Berk, J. H. Lang, E. C. Lasser, and R. C. Dunn, *Amer. J. Roentgenol., Radium Ther. Nucl. Med.*, **114**, 767(1972); through *Chem. Abstr.*, **77**, 42053b(1972).
(1428) K. Asghar and S. Riegelman, *Arch. Int. Pharmacodyn. Ther.*, **194**, 18(1971); through *Chem. Abstr.*, **76**, 107974s(1972).
(1429) M. W. Neathery, S. Rachmat, W. J. Miller, R. P. Gentry, and D. M. Blackmon, *Proc. Soc. Exp. Biol. Med.*, **139**, 953(1972).
(1430) S. Tomizawa and K. Kagawa, *Oyo Yakuri*, **5**, 531(1971); through *Chem. Abstr.*, **76**, 108181t(1972).
(1431) E. Gladtke, *Deut. Apoth.-Ztg.*, **112**, 874(1972); through *Chem. Abstr.*, **77**, 92758u(1972).
(1432) E. A. Govorovich and N. S. Bogomolova, *Antibiotiki (Moscow)*, **16**, 1010(1971); through *Chem. Abstr.*, **76**, 68030j(1972).
(1433) A. M. Mattocks and S. C. Penzotti, *J. Pharm. Sci.*, **61**, 475 (1972).
(1434) E. H. M. Eassa, *U. S. At. Energy Comm.*, UR-49-1462 (1971); from *Nucl. Sci. Abstr.*, **25**, 42617(1971); through *Chem. Abstr.*, **76**, 41887g(1972).
(1435) P. D. Hart and S. N. Payne, *Brit. J. Pharmacol.*, **43**, 190 (1971); through *Chem. Abstr.*, **76**, 41883c(1972).
(1436) K. H. Froemming, R. Sandmann, and H. Lix, *Pharm. Ind.*, **33**, 766(1971); through *Chem. Abstr.*, **76**, 135524p(1972).
(1437) J. C. Venter, J. E. Dixon, P. R. Maroko, and N. O. Kaplan, *Proc. Nat. Acad. Sci. USA*, **69**, 1141(1972); through *Chem. Abstr.*, **77**, 56468r(1972).
(1438) M. Marzuez and D. J. Roberts, *J. Pharm. Pharmacol.*, **24**, 658(1972).
(1439) E. A. Hartshorn, *Drug Intel. Clin. Pharm.*, **5**, 388(1971); through *Chem. Abstr.*, **76**, 135430e(1972).
(1440) D. A. Roe, D. B. McCormick, and R. Lin, *J. Pharm. Sci.*, **61**, 1081(1972).
(1441) B. Lotti and M. Galloni, *Farmaco, Ed. Prat.*, **27**, 275(1972); through *Chem. Abstr.*, **77**, 56361a(1972).
(1442) M. Szekerke, R. Wade, and M. E. Whisson, *Neoplasma*, **19**, 199(1972); through *Chem. Abstr.*, **77**, 83744j(1972).
(1443) *Ibid.*, **19**, 211(1972); through *Chem. Abstr.*, **77**, 83745k (1972).
(1444) P. Kahela, A. Perala-Suominen, M. Ahomaa, and P. Voutilainen, *Farm. Aikak.*, **80**, 331(1971); through *Chem. Abstr.*, **76**, 94592p(1972).
(1445) J. L. Burton, *J. Soc. Cosmet. Chem.*, **23**, 241(1972).
(1446) J. T. Henderson, R. R. G. Warwick, J. D. Simpson, and D. J. C. Shearman, *Lancet*, **2**, 241(1972).
(1447) H. Hoffmann, *Acta Biol. Med. Ger.*, **26**, 1229(1971); through *Chem. Abstr.*, **76**, 94715f(1972).
(1448) N. I. Gold and J. F. Crigler, Jr., *J. Clin. Endocrinol. Metab.*, **34**, 1025(1972).
(1449) L. F. Krabill and J. P. Hannon, *Amer. J. Physiol.*, **222**, 458 (1972).
(1450) C. Y. C. Pak, D. A. East, L. J. Sanzenbacher, C. S. Delea, and F. C. Bartter, *J. Clin. Endocrinol. Metab.*, **35**, 261(1972).
(1451) I. M. Coupar and I. McColl, *J. Pharm. Pharmacol.*, **24**, 254 (1972).
(1452) E. Anselmi and J. Larralde, *Rev. Espan. Fisiol.*, **27**, 375 (1971); through *Chem. Abstr.*, **76**, 121711k(1972).
(1453) W. F. Caspary and W. Creutzfeldt, *Diabetologia*, **7**, 379 (1971); through *Chem. Abstr.*, **76**, 121436z(1972).
(1454) J. D. Teale and A. H. G. Love, *Biochem. Pharmacol.*, **21**, 1839(1972).
(1455) T. Kumura, H. Sezaki, and K. Kakemi, *Chem. Pharm. Bull.*, **20**, 1656(1972).
(1456) A. D. J. Watson, *J. Small Anim. Pract.*, **13**, 153(1972); through *Chem. Abstr.*, **77**, 56672c(1972).
(1457) *Ibid.*, **13**, 147(1972); through *Chem. Abstr.*, **77**, 56673d (1972).
(1458) A. M. McBean, P. Compaore, W. M. McCormak, A. N. Agle, and S. O. Foster, *Lancet*, **1**, 527(1972).
(1459) A. H. Beckett, J. W. Gorrod, and D. C. Taylor, *J. Pharm. Pharmacol.*, **24**, 65P(1972).
(1460) H. J. Dengler, *Arzneim.-Forsch.*, **22**, 297(1972); through *Chem. Abstr.*, **77**, 56227m(1972).
(1461) J. Zaroslinksi, R. Brown, and L. Possley, *Arch. Int. Pharmacodyn. Ther.*, **195**, 185(1972); through *Chem. Abstr.*, **76**, 148929z(1972).
(1462) M. Gibaldi and B. Grundhofer, *J. Pharm. Sci.*, **61**, 116 (1972).
(1463) K. S. Pelzmann and R. N. Havemeyer, *ibid.*, **61**, 110 (1972).
(1464) S. Kojima, R. B. Smith, W. G. Crouthamel, and J. T. Doluisio, *ibid.*, **61**, 1061(1972).
(1465) H. Ochsenfahrt, *Gastrointest. Motility, Int. Symp. Motility GI-Tract*, **1969**, 204; through *Chem. Abstr.*, **77**, 56385m(1972).
(1466) T. Nadai, R. Kondo, A. Tatematsu, and H. Sezaki, *Chem. Pharm. Bull.*, **20**, 1139(1972).
(1467) W. Klaus, *Egypt. Pharm. J.*, **53**, 229(1971); through *Chem. Abstr.*, **76**, 158240g(1972).
(1468) E. Frömter and J. Diamond, *Nature*, **235**, 9(1972).
(1469) F. Alhaique, M. Marchetti, F. M. Riccieri, and E. Santucci, *Farmaco, Ed. Sci.*, **27**, 145(1972); through *Chem. Abstr.*, **76**, 148815j(1972).
(1470) M. P. Short and C. T. Rhodes, *Nature (London), New Biol.*, **236**, 44(1972); through *Chem. Abstr.*, **77**, 13941x(1972).
(1471) R. K. Ockner, J. A. Manning, R. B. Poppengausen, and W. K. L. Ho, *Science*, **177**, 56(1972).
(1472) E. Suzuki, M. Tsukigi, S. Muranishi, H. Sezaki, and K. Kakemi, *J. Pharm. Pharmacol.*, **24**, 138(1972).
(1473) S. I. Bhuta, *Diss. Abstr., Int. B*, **33**, 1173(1972).
(1474) K. Kakemi, H. Sezaki, S. Muranishi, H. Ogata, and S. Isemura, *Chem. Pharm. Bull.*, **20**, 708(1972).
(1475) K. Kakemi, H. Sezaki, S. Muranishi, H. Ogata, and K. Giga, *ibid.*, **20**, 715(1972).
(1476) K. Kakemi, H. Sezaki, H. Ogata, and C. Nagai, *ibid.*, **20**, 1053(1972).
(1477) M. A. Friedman, E. J. Greene, and S. S. Epstein, *J. Pharm. Sci.*, **61**, 1492(1972).
(1478) M. J. Bartek, J. A. LaBudde, and H. I. Maibach, *J. Invest. Dermatol.*, **58**, 114(1972).
(1479) K. Okumura, H. Sezaki, and K. Kakemi, *Chem. Pharm. Bull.*, **20**, 1607(1972).
(1480) R. Levy, *Diss. Abstr., Int. B*, **33**, 1472(1972).
(1481) R. H. Levy and M. Rowland, *J. Pharm. Sci.*, **61**, 1263 (1972).
(1482) S. J. Enna and L. S. Schanker, *Amer. J. Physiol.*, **222**, 409 (1972).
(1483) *Ibid.*, **223**, 1227(1972).
(1484) W. F. Stanaszek and B. Ecanow, *J. Pharm. Sci.*, **61**, 860 (1972).
(1485) R. R. Levine, *Top. Med. Chem.*, **4**, 27(1971); through *Chem. Abstr.*, **76**, 107744s(1972).
(1486) A. C. Moffat, *ibid.*, **4**, 1(1971); through *Chem. Abstr.*, **76**, 167743r(1972).

(1487) E. Schoffeniels, *Fundam. Biochem. Pharmacol.*, **1971,** 195; through *Chem. Abstr.*, **76,** 121290x(1972).
(1488) K. J. Ivey and J. A. Clifton, *J. Lab. Clin. Med.*, **78,** 753 (1971); through *Chem. Abstr.*, **76,** 68291v(1972).
(1489) S. J. Birge, H. R. Gilbert, and L. V. Avioli, *Science*, **176,** 168(1972).
(1490) H. Kunze, G. Rehbock, and W. Vogt, *Naunyn-Schmiedeberg's Arch. Pharmacol.*, **273,** 331(1972); through *Chem. Abstr.*, **77,** 121966t(1972).
(1491) S. A. Kaplan and S. Cotler, *J. Pharm. Sci.*, **61,** 1361(1972).
(1492) R. Lev and D. Orlic, *Science*, **177,** 522(1972).
(1493) A. Kato, *Nichidai Igaku Zasshi*, **30,** 972(1971); through *Chem. Abstr.*, **76,** 94422h(1972).
(1494) M. Nakanishi, A. Tsuda, R. Takamatsu, and K. Kishiro, *Oyo Yakuri*, **4,** 479(1970); through *Chem. Abstr.*, **76,** 80961w (1972).
(1495) J. Bergmark, A. Carlsson, A. K. Granerus, R. Jagenburg, T. Magnusson, and A. Svanborg, *Naunyn-Schmiedeberg's Arch. Pharmacol.*, **272,** 437(1972); through *Chem. Abstr.*, **77,** 43009s (1972).
(1496) D. F. Evered and H. S. Selhi, *Biochem. J.*, **126,** 26P(1972); through *Chem. Abstr.*, **76,** 135526r(1972).
(1497) R. T. Reinke and R. N. Berk, *Amer. J. Roentgenol., Radium Ther. Nucl. Med.*, **113,** 578(1971); through *Chem. Abstr.*, **76,** 94657p(1972).
(1498) T. Komai and H. Shindo, *J. Vitaminol.*, **18,** 55(1972); through *Chem. Abstr.*, **77,** 56341u(1972).
(1499) G. Embery and P. H. Dugard, *J. Invest., Dermatol.*, **57,** 308(1971); through *Chem. Abstr.*, **76,** 94821n(1972).
(1500) N. H. Creasey, A. C. Allenby, and C. Schock, *Brit. J. Dermatol.*, **85,** 368(1971); through *Chem. Abstr.*, **77,** 609v(1972).
(1501) M. Ito, *Nippon Yakubutsugaku Zasshi*, **66,** 618(1970); through *Chem. Abstr.*, **76,** 41991m(1972).
(1502) F. I. Kolpakov and S. A. Popkov, *Vestn. Dermatol. Venerol.*, **46,** 42(1972); through *Chem. Abstr.*, **77,** 190267h(1972).
(1503) N. V. Latushkina, *ibid.*, **45,** 54(1971); through *Chem. Abstr.*, **77,** 693t(1972).
(1504) M. Washitake, T. Yajima, T. Anmo, T. Arita, and R. Hori, *Chem. Pharm. Bull.*, **20,** 2429(1972).
(1505) J. H. Kim, K. Green, M. Martinez, and D. Paton, *Exp. Eye Res.*, **12,** 231(1971); through *Chem. Abstr.*, **76,** 95282z(1972).
(1506) K. Green and A. Tonjum, *Amer. J. Ophthalmol.*, **72,** 897 (1971); through *Chem. Abstr.*, **76,** 81039p(1972).
(1507) G. Levy, L. L. Mosovich, J. E. Allen, and S. J. Yaffe, *J. Pharm. Sci.*, **61,** 143(1972).
(1508) G. Czok and H. G. Dammann, *J. Pharm. Pharmacol.*, **24,** 820(1972).
(1509) J. A. Nelson, L. Z. Benet, and R. J. Goldberg, *ibid.*, **24,** 993(1972).
(1510) R. A. Runkel, K. S. Kraft, G. Boost, H. Sevelius, E. Forchielli, R. Hill, R. Magoun, J. B. Szakacs, and E. Segre, *Chem. Pharm. Bull.*, **20,** 1457(1972).
(1511) R. Runkel, M. Chaplin, G. Boost, E. Serge, and E. Forchielli, *J. Pharm. Sci.*, **61,** 703(1972).
(1512) B. Beerman, K. Hellström, and A. Rose'n, *Clin. Pharmacol. Ther.*, **13,** 212(1972).
(1513) Y. Ono, N. Tatewaki, A. Okita, and Y. Katsura, *Yakugaku Zasshi*, **92,** 592(1972).
(1514) H. Schröder and D. E. S. Campbell, *Clin. Pharmacol. Ther.*, **13,** 539(1972).
(1515) H. L. Friedman and R. I. H. Wang, *J. Pharm. Sci.*, **61,** 1663(1972).
(1516) E. F. Lemanowicz, *Diss. Abstr., Int. B*, **33,** 1173(1972).
(1517) R. E. Notari, J. L. DeYoung, and R. H. Reuning, *J. Pharm. Sci.*, **61,** 135(1972).
(1518) V. F. Smolen, *Can. J. Pharm. Sci.*, **7,** 1(1972).
(1519) *Ibid.*, **7,** 7(1972).
(1520) M. Moriyama, M. Saito, S. Awazu, M. Hanano, and H. Nogami, *Yakugaku Zasshi*, **91,** 1217(1971).
(1521) T. Fuwa, T. Iga, M. Hanano, H. Nogami, and M. Kashima, *ibid.*, **91,** 1223(1971).
(1522) H. C. Heinrich, H. Bartels, E. E. Gabbe, G. Kugler, K. H. Oppitz, R. Kleinfeld, and K. Mezey, *Arzneim.-Forsch.*, **22,** 1091 (1972); through *Chem. Abstr.*, **77,** 159981g(1972).
(1523) I. L. Shannon and E. J. Edmonds, *Arch. Oral Biol.*, **17,** 1303(1972); through *Chem. Abstr.*, **77,** 160278q(1972).
(1524) W. J. Decker, W. A. Goldsmith, R. C. Mills, and R. J. Banez, *Toxicol. Appl. Pharmacol.*, **21,** 331(1972).
(1525) U. Consbruch and H. Koufen, *Pharmakopsychiat./Neuro-Psychopharmakol.*, **5,** 104(1972); through *Chem. Abstr.*, **77,** 56365e (1972).
(1526) V. F. Smolen and R. I. Poust, *J. Pharm. Sci.*, **61,** 1102 (1972).
(1527) P. C. H. Newbold and R. B. Stoughton, *J. Invest. Dermatol.*, **58,** 319(1972).
(1528) S. R. Walker, M. E. Evans, A. J. Richards, and J. W. Paterson, *J. Pharm. Pharmacol.*, **24,** 525(1972).
(1529) S. R. Walker, A. J. Richards, and J. W. Paterson, *Biochem. J.*, **125,** 27p(1971); through *Chem. Abstr.*, **76,** 80967c(1972).
(1530) S. R. Walker, M. E. Evans, A. J. Richards, and J. W. Paterson, *Clin. Pharmacol. Ther.*, **13,** 861(1972).
(1531) T. Lawrence, *Top. Med. Chem.*, **4,** 253(1971); through *Chem. Abstr.*, **76,** 107746u(1972).
(1532) M. B. Roberfroid and P. A. Dumont, *J. Antibiot., Ser. A*, **25,** 30(1972).
(1533) I. R. Peake, H. G. Windmueller, and J. G. Bieri, *Biochim. Biophys. Acta*, **260,** 679(1972); through *Chem. Abstr.*, **77,** 43024t(1972).
(1534) C. D. Gerson, *Mt. Sinai J. Med., New York*, **39,** 343 (1972); through *Chem. Abstr.*, **77,** 149918c(1972).
(1535) M. Yoshikawa and Y. Sato, *Yakugaku Zasshi*, **92,** 551 (1972).
(1536) R. H. Bishara, G. S. Born, and J. E. Christian, *J. Pharm. Sci.*, **61,** 1912(1972).
(1537) J. Shimmins, F. C. Gillespie, J. S. Orr, D. A. Smith, and W. D. Alexander, *Advan. Biosci.*, **5,** 157(1969); through *Chem. Abstr.*, **76,** 121410m(1972).
(1538) M. G. Bogaert and M. T. Rosseel, *J. Pharm. Pharmacol.*, **24,** 737(1972).
(1539) M. Otsuka, S. Nakamura, and Y. Sato, *Yakugaku Zasshi*, **92,** 986(1972).
(1540) G. N. Smith, D. Mollison, B. Griffiths, and P. L. Mollison, *Lancet*, **1,** 1208(1972).
(1541) V. Lebedenko, N. G. Shubenkin, I. S. Azhgikhin, A. Z. Knizhnik, and P. L. Senov, *Farmatsiya (Moscow)*, **21,** 22(1972); through *Chem. Abstr.*, **77,** 43387p(1972).
(1542) S. Y. Papu, V. F. Davydov, and I. S. Azhgikhin, *ibid.*, **21,** 52(1972); through *Chem. Abstr.*, **77,** 147604y(1972).
(1543) M. Johnsgard and Y. Torud, *Norg. Apotekerforen. Tidsskr.*, **79,** 464(1971); through *Chem. Abstr.*, **76,** 148685s(1972).
(1544) R. G. Weigand and A. H. C. Chun, *J. Pharm. Sci.*, **61,** 425(1972).
(1545) S. M. Bell, *Med. J. Aust.*, **2,** 1280(1971); through *Chem. Abstr.*, **76,** 135522m(1972).
(1546) H. P. Ojiambo, *East Afr. Med. J.*, **48,** 318(1971); through *Chem. Abstr.*, **76,** 135685s(1972).
(1547) H. Niwa and T. Nakayama, *Oyo Yakuri*, **5,** 669(1972); through *Chem. Abstr.*, **76,** 148724d(1972).
(1548) A. Rubin, B. E. Rodda, P. Warrick, A. S. Ridolfo, and C. M. Gruber, Jr., *J. Pharm. Sci.*, **61,** 739(1972).
(1549) D. G. Shand and R. E. Rangno, *Pharmacology*, **7,** 159 (1972); through *Chem. Abstr.*, **77,** 97005f(1972).
(1550) I. I. Prokhorova and S. I. Eidel'shtein, *Strukt. Funkts. Gisto-Gematicheskikh Bar'erov, Mater. Soveshch. Probl. Gisto-Gematicheskikh Bar'erov. 4th*, **1969,** 129; through *Chem. Abstr.*, **76,** 148684r(1972).
(1551) O. Matsuba, *Tokyo Jikeikai Ika Daigaku Zasshi*, **86,** 541 (1971); through *Chem. Abstr.*, **77,** 56701m(1972).
(1552) K. Ogli, *Med. J. Osaka Univ.*, **22,** 33(1971); through *Chem. Abstr.*, **77,** 147388f(1972).
(1553) M. Washitake, T. Yajima, T. Anmo, T. Arita, and R. Hori, *Chem. Pharm. Bull.*, **20,** 2429(1972).
(1554) L. G. Hart, D. H. McCurdy, and R. Teichman, *Proc. Soc. Exp. Biol. Med.*, **140,** 715(1972); through *Chem. Abstr.*, **77,** 43384k(1972).
(1555) M. Mayersohn, *Eur. J. Pharmacol.*, **19,** 140(1972); through *Chem. Abstr.*, **77,** 109263d(1972).
(1556) M. Rowland, S. Riegelman, P. A. Harris, and S. D. Sholkoff, *J. Pharm. Sci.*, **61,** 379(1972).
(1557) A. H. Beckett and J. A. Salmon, *J. Pharm. Pharmacol.*, **24,** 108(1972).
(1558) F. H. Dost and H. M. Von Hattingbert, *Pharm. Ztg.*, **117,** 6(1972); through *Chem. Abstr.*, **77,** 54k(1972).
(1559) J. M. Van Rossum, *Med. Chem., Ser. Monogr.*, **11,** 469

(1971); through *Chem. Abstr.*, **76,** 121357z(1972).
(1560) F. Gregoire, *J. Pharm. Belg.*, **27,** 355(1972); through *Chem. Abstr.*, **77,** 79486j(1972).
(1561) A. Danek, *Farm. Pol.*, **28,** 485(1972); through *Chem. Abstr.*, **77,** 96656g(1972).
(1562) E. R. Garrett, *Advan. Biosci.*, **5,** 7(1969); through *Chem. Abstr.*, **76,** 121376e(1972).
(1563) Z. Modr and K. Dvoracek, *ibid.*, **5,** 219(1969); through *Chem. Abstr.*, **76,** 121382d(1972).
(1564) U. Elste, *Krankenhaus-Apoth.*, **22,** 9(1972); through *Chem. Abstr.*, **77,** 56271w(1972).
(1565) W. J. O'Reilly, *Can. J. Pharm. Sci.*, **7,** 66(1972).
(1566) H. Gillman, *Arzneim.-Forsch.*, **22,** 283(1972); through *Chem. Abstr.*, **77,** 56224h(1972).
(1567) A. Bieder and J. Gaillot, *Ann. Pharm. Fr.*, **29,** 619(1971); through *Chem. Abstr.*, **77,** 53j(1972).
(1568) R. Fumagalli, *Metab. Eff. Nicotinic Acid Its Deriv., Proc. Workshop*, **1970,** 33; through *Chem. Abstr.*, **77,** 159931r(1972).
(1569) A. Herz and H. J. Teschemacher, *Advan. Drug Res.*, **6,** 79(1971); through *Chem. Abstr.*, **76,** 148640y(1972).
(1570) J. H. Nodine, *Advan. Biosci.*, **5,** 231(1969); through *Chem. Abstr.*, **76,** 121383e(1972).
(1571) A. Locker, *ibid.*, **5,** 115(1969); through *Chem. Abstr.*, **76,** 121380b(1972).
(1572) S. Riegelman, *Aspirin, Platelets Stroke*, **1971,** 105; through *Chem. Abstr.*, **76,** 135413b(1972).
(1573) E. Rudzitis and Z. V. Nefedova, *Antibiotiki (Moscow)*, **16,** 1113(1971); through *Chem. Abstr.*, **76,** 94378y(1972).
(1574) F. Gregoire, *J. Pharm. Belg.*, **27,** 99(1972); through *Chem. Abstr.*, **76,** 148611q(1972).
(1575) G. Hitzenberger, *Verh. Deut. Ges. Inn. Med.*, **77,** 1412 (1971); through *Chem. Abstr.*, **77,** 13795c(1972).
(1576) I. Janku, *Fundam. Biochem. Pharmacol.*, **1971,** 203; through *Chem. Abstr.*, **76,** 121291y(1972).
(1577) G. Stuettgen, *Arzneim.-Forsch.*, **22,** 324(1972); through *Chem. Abstr.*, **77,** 121925d(1972).
(1578) J. C. Loo, *Diss. Abstr., Int. B*, **33,** 1472(1972).
(1579) A. R. DiSanto and J. G. Wagner, *J. Pharm. Sci.*, **61,** 552 (1972).
(1580) L. Z. Benet, *ibid.*, **61,** 536(1972).
(1581) L. Saunders and T. Natunen, *J. Pharm. Pharmacol.*, **24,** 94P(1972).
(1582) P. A. Mitenko and R. I. Ogilvie, *Clin. Pharmacol. Ther.*, **13,** 329(1972).
(1583) M. C. Meyer, *Arch. Int. Pharmacodyn. Ther.*, **193,** 294 (1971); through *Chem. Abstr.*, **76,** 81349q(1972).
(1584) T. Tsuchiya and G. Levy, *J. Pharm. Sci.*, **61,** 541(1972).
(1585) T. G. Theofanous and V. F. Smolen, *ibid.*, **61,** 980(1972).
(1586) W. J. Jusko and M. Gibaldi, *ibid.*, **61,** 1270(1972).
(1587) M. Gibaldi and D. Perrier, *ibid.*, **61,** 952(1972).
(1588) J. E. Axelson and M. Gibaldi, *ibid.*, **61,** 404(1972).
(1589) W. J. O'Reilly, P. A. Pitt, and A. J. Ryan, *Brit. J. Pharmacol.*, **43,** 167(1971); through *Chem. Abstr.*, **76,** 41816h(1972).
(1590) Y. Dormard and J. C. Levron, *J. Eur. Toxicol.*, **5,** 43(1972); through *Chem. Abstr.*, **77,** 159999u(1972).
(1591) M. Gibaldi, G. Levy, and W. Hayton, *Anesthesiology*, **36,** 213(1972); through *Chem. Abstr.*, **77,** 14394h(1972).
(1592) M. Gibaldi and G. Levy, *J. Pharm. Sci.*, **61,** 567(1972).
(1593) G. R. Bourne and H. E. Barber, *J. Pharm. Pharmacol.*, **24,** 532(1972).
(1594) G. Acocella, V. Pagani, and F. B. Nicolis, *Boll. Chim. Farm.*, **111,** 108(1972); through *Chem. Abstr.*, **77,** 56382h(1972).
(1595) A. R. DiSanto and J. G. Wagner, *J. Pharm. Sci.*, **61,** 598 (1972).
(1596) *Ibid.*, **61,** 1090(1972).
(1597) *Ibid.*, **61,** 1086(1972).
(1598) K. A. McMahon and W. J. O'Reilly, *J. Pharm. Sci.*, **61,** 518(1972).
(1599) *Ibid.*, **61,** 524(1972).
(1600) T. Tsuchiya and G. Levy, *J. Pharm. Sci.*, **61,** 800(1972).
(1601) G. Levy, T. Tsuchiya, and L. P. Amsel, *Clin. Pharmacol. Ther.*, **13,** 258(1972).
(1602) F. R. Sidell, W. A. Groff, and A. Kaminskis, *J. Pharm. Sci.*, **61,** 1136(1972).
(1603) A. Karim, E. Ranney, K. L. Evensen, and M. L. Clark, *Clin. Pharmacol. Ther.*, **13,** 407(1972).
(1604) A. R. Nissenson, N. W. Levin, and R. H. Parker, *ibid.*, **13,** 887(1972).
(1605) U. Ryderb, J. Buijten, and A. Neri, *J. Pharm. Pharmacol.*, **24,** 651(1972).
(1606) A. Parera and J. M. Sune, *Ars Pharm.*, **12,** 215(1971); through *Chem. Abstr.*, **77,** 39135n(1972).
(1607) C. R. Dunn and R. N. Berk, *Amer. J. Roentgenol., Radium Ther. Nucl. Med.*, **114,** 758(1972); through *Chem. Abstr.*, **77,** 43052a (1972).
(1608) D. W. Yesair, E. Schwartzbach, D. Shuck, E. P. Denine, and M. A. Asbell, *Cancer Res.*, **32,** 1177(1972); through *Chem. Abstr.*, **77,** 147414m(1972).
(1609) N. Gheorghe, *Rev. Roum. Physiol.*, **9,** 145(1972); through *Chem. Abstr.*, **77,** 56723v(1972).
(1610) D. Zekorn, *Bibl. Haematol. (Basel)*, **1969,** 131; through *Chem. Abstr.*, **76,** 41932t(1972).
(1611) H. Nitschmann and H. R. Stoll, *ibid.*, **1969,** 152; through *Chem. Abstr.*, **76,** 41821f(1972).
(1612) R. Hess, A. Herz, and K. Friedel, *J. Pharmacol. Exp. Ther.*, **179,** 474(1971); through *Chem. Abstr.*, **76,** 81088d(1972).
(1613) D. Henschler, K. Hempel, B. Schultze, and W. Maurer, *Arzneim.-Forsch.*, **21,** 1682(1971); through *Chem. Abstr.*, **76,** 94584n (1972).
(1614) E. Heinze and H. G. Kampffmeyer, *Klin. Wochenschr.*, **49,** 1146(1971); through *Chem. Abstr.*, **76,** 30668k(1972).
(1615) T. B. Gottlieb, R. C. Thomas, and C. A. Chidsey, *Clin. Pharmacol. Ther.*, **13,** 436(1972).
(1616) J. W. Jenne, E. Wyze, F. S. Rood, and F. M. MacDonald, *ibid.*, **13,** 349(1972).
(1617) D. G. Kaiser and E. M. Glenn, *J. Pharm. Sci.*, **61,** 1908 (1972).
(1618) N. Zoellner and W. Kaiser, *Res. Exp. Med.*, **158,** 89(1972); through *Chem. Abstr.*, **77,** 159991k(1972).
(1619) E. Arena, N. D'Alessandro, L. Dusonchet, N. Gebbia, F. Gerbasi, M. Palazzoadriano, A. Rainieri, L. Rausa, and E. Tubaro, *G. Ital. Chemioter.*, **17,** 223(1970); through *Chem. Abstr.*, **77,** 43345y(1972).
(1620) K. L. Rominger and W. Pollmann, *Arzneim.-Forsch.*, **22,** 1190(1972); through *Chem. Abstr.*, **77,** 159983j(1972).
(1621) W. A. Cressman, N. L. Renzi, and A. C. Bartholomay, *J. Pharm. Sci.*, **61,** 1170(1972).
(1622) N. G. M. Bishara, A. David, and R. G. Henein, *Proc. Conf. Appl. Phys. Chem., 2nd*, **2,** 653(1971); through *Chem. Abstr.*, **76,** 144769z(1972).
(1623) R. G. Henein, A. David, and N. G. M. Bishara, *ibid.*, **2,** 663(1971); through *Chem. Abstr.*, **76,** 144774x(1972).
(1624) N. G. M. Bishara, *Gyogyszereszet*, **16,** 121(1972); through *Chem. Abstr.*, **77,** 66122n(1972).
(1625) A. H. Beckett, J. W. Gorrod, and P. Jenner, *J. Pharm. Pharmacol.*, **24,** 115(1972).
(1626) F. G. Cantelli and M. E. Fracasso, *Boll. Soc. Ital. Biol. Sper.*, **47,** 575(1971); through *Chem. Abstr.*, **76,** 148710w(1972).
(1627) T. Iga, S. Awazu, and H. Nogami, *Chem. Pharm. Bull.*, **20,** 349(1972).
(1628) G. Fuelgraff, *Arzneim.-Forsch.*, **22,** 1231(1972); through *Chem. Abstr.*, **77,** 159967g(1972).
(1629) M. M. Abdel-Monem, P. A. Harris, and P. S. Portoghese, *J. Med. Chem.*, **15,** 706(1972).
(1630) P. R. Yarnell, R. L. Bell, P. Ng, and W. T. Gromley, *Clin. Pharmacol. Ther.*, **13,** 558(1972).
(1631) A. L. Levy and S. K. Levy, *Biochem. Med.*, **6,** 127(1972); through *Chem. Abstr.*, **77,** 56320m(1972).
(1632) K. Ikeda, Y. Kurono, and T. Tukamoto, *Chem. Pharm. Bull.*, **20,** 863(1972).
(1633) W. J. Jusko, G. P. Lewis, and L. W. Dittert, *Chemotherapy*, **17,** 109(1972); through *Chem. Abstr.*, **76,** 121416t(1972).
(1634) A. H. Beckett, E. V. B. Shenoy, and J. A. Salmon, *J. Pharm. Pharmacol.*, **24,** 194(1972).
(1635) D. S. Davies and S. S. Thorgeirsson, *Acta Pharmacol. Toxicol., Suppl.*, **29,** 181(1971); through *Chem. Abstr.*, **76,** 121920c (1972).
(1636) M. C. B. Van Oudtshoorn and F. J. Potgieter, *J. Pharm. Pharmacol.*, **24,** 357(1972).
(1637) J. M. Hayward, *J. Hosp. Pharm.*, **29,** 243(1971); through *Chem. Abstr.*, **76,** 30479z(1972).
(1638) B. E. Rodda, *Arch. Int. Pharmacodyn. Ther.*, **194,** 290 (1971); through *Chem. Abstr.*, **76,** 76399b(1972).

(1639) S. A. Kaplan, R. E. Weinfeld, C. W. Abruzzo, and M. Lewis, *J. Pharm. Sci.*, **61**, 773(1972).
(1640) K. F. Funk, *Acta Biol. Med. Ger.*, **27**, 611(1971); through *Chem. Abstr.*, **76**, 148936z(1972).
(1641) D. D. Reedler, B. M. Jackson, E. N. Brandt, Jr., and J. C. Thompson, *Amer. J. Physiol.*, **222**, 1571(1972).
(1642) H. Roepke, *Advan. Biosci.*, **1**, 61(1967); through *Chem. Abstr.*, **76**, 121434x(1972).
(1643) D. S. Zaharko, *Cancer Chemother. Rep., Part 3*, **3**, 21 (1972); through *Chem. Abstr.*, **77**, 83381p(1972).
(1644) W. C. Werkheiser, *Ann. N.Y. Acad. Sci.*, **186**, 343(1971); through *Chem. Abstr.*, **76**, 121934k(1972).
(1645) D. S. Hewick, *J. Pharm. Pharmacol.*, **24**, 661(1972).
(1646) A. Breckenridge and M. L. Orme, *Life Sci.*, **11**, 337(1972); through *Chem. Abstr.*, **77**, 43227m(1972).
(1647) J. J. Coffey, *J. Pharm. Sci.*, **61**, 138(1972).
(1648) H. B. Hucker, S. C. Stauffer, and S. E. White, *ibid.*, **61**, 1490(1972).
(1649) B. M. Boulos, W. L. Jenkins, and L. E. Davis, *Amer. J. Vet. Res.*, **1972**, 943; through *Chem. Abstr.*, **77**, 56366f(1972).

ACKNOWLEDGMENTS AND ADDRESSES

Received from the * *Pharmacy Research Unit, Pharmaceutical Research and Development Division, The Upjohn Co., Kalamazoo, MI 49001*, and the † *Operations Division, Syntex Laboratories, Inc., Palo Alto, CA 94304*

▲ To whom inquiries should be directed.

RESEARCH ARTICLES

Carbocyclic Analogs of 6-Substituted Purine Ribonucleosides and of Adenosine Ribonucleotides

Y. FULMER SHEALY▲ and JOE D. CLAYTON

Abstract □ New analogs of 6-substituted purine ribonucleosides in which the furanose ring is replaced by a cyclopentane ring were synthesized. The cyclopentane (carbocyclic) analog of 6-chloropurine ribonucleoside was obtained in pure form and was used to prepare analogs having a methylamino, dimethylamino, hydroxylamino, or methoxy group at position 6 of the purine ring. The availability of the pure 6-chloropurine derivative also permitted improved syntheses of the adenosine and 6-(methylthio)purine ribonucleoside analogs, which had been prepared previously. The ribonucleoside analogs having the chloro, methylamino, hydroxylamino, or methoxy group at position 6 were cytotoxic to neoplastic cells (human epidermoid carcinoma No. 2) in culture, but these compounds were less active than the adenosine analog. In tests against leukemia L-1210 in mice, all of the new and the previously synthesized 6-substituted purine ribonucleoside analogs were administered in a single dose (Day 1 or 2), and most were also administered daily (*q.d.* 1–9) at several dose levels. There was no evidence of activity in these tests. The racemic carbocyclic analogs of adenylic acid and of 3′,5′-adenosine monophosphate (cyclic) were prepared from the adenosine analog. These nucleotide analogs were also cytotoxic.

Keyphrases □ Cyclopentane analogs of 6-substituted purine ribonucleosides and adenosine ribonucleotides—synthesis, cytotoxicity □ Carbocyclic analogs of 6-substituted purine nucleosides and adenosine ribonucleotides—synthesis, cytotoxicity □ Purine ribonucleosides, 6-substituted—synthesis of cyclopentane analogs, cytotoxicity □ Adenosine ribonucleotides, 6-substituted—synthesis of cyclopentane analogs, cytotoxicity □ Cytotoxicity—synthesis, evaluation of cyclopentane analogs of 6-substituted purine ribonucleosides and adenosine ribonucleotides

Nucleoside analogs in which a cyclopentane ring replaces the furanose ring may be termed carbocyclic analogs. The racemic[1], carbocyclic analog (II, C-Ado[2]) of adenosine (I) has been synthesized (1) by a multistep route from norbornadiene. The carbocyclic analogs (III–V) of inosine and of the anticancer agents 6-mercaptopurine ribonucleoside and 6-(methylthio)purine ribonucleoside were also prepared (2) from the precursors of II. The carbocyclic analogs of 2′- and 3′-deoxyadenosine were synthesized by similar routes (3); the analog of a pyrimidine deoxyribonucleoside, thymidine, had been prepared earlier by a different method (4).

Carbocyclic analogs, having a stable carbon–nitrogen bond instead of a glycosidic bond at position 9 of the purine ring, should not be subject to cleavage by purine nucleoside phosphorylases or hydrolases, but the similarity of their structures to nucleosides endows the carbocyclic analogs with the potential to function either as substrates for, or as inhibitors of, other enzymes that metabolize nucleosides. Biochemical studies show that this potential can, in fact, be realized. Bennett and co-

[1] Structures II–XVI depict one enantiomer of the racemic form that was actually obtained.

[2] (±)-*trans*-3-(6-Amino-9*H*-purin-9-yl)-*trans*-5-(hydroxymethyl)-*cis*-1,2-cyclopentanediol. For the sake of brevity, the term C-Ado was employed in reports of biochemical studies (5, 6). In earlier publications (1, 2), C-Ado was designated (±)- or DL-9-[β-(2α,3α-dihydroxy-4β-(hydroxymethyl)cyclopentyl)] adenine.