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REVIEW ARTICLE

Pharmaceutical Sciences—1975: Literature Review of Pharmaceutics II ▲

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Keyphrases □ Pharmaceutical sciences—1975 literature review of pharmaceutics □ Technology, pharmaceutical—sterility, dosage forms, cosmetics, packaging equipment, dental products, biomedical devices, 1975 literature review □ Stability—solids, solutions, injectable products, antibiotics, and vitamins, kinetics, 1975 literature review □ Dosage forms—tablets, suspensions, emulsions, suppositories, aerosols, controlled-release devices, 1975 literature review □ Cosmetics—formulation and technology, microbiological contamination, 1975 literature review □ Instrumentation—in pharmaceutical technology, 1975 literature review □ Literature review—pharmaceutical sciences, 1975

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PHYSICAL PHARMACY

Several articles discussed the polymorphic characteristics of drugs. Of the two polymorphic forms of homatropine hydrochloride described, Form I was found to be metastable whereas Form II was stable at room temperature (817). Slow heating during melting-point determinations converted Form II to Form I. Polymorphs of testosterone were analyzed by IR spectroscopy, differential scanning calorimetry, and thermal analysis (818). Upon heating, all forms reverted to Form I. Differential scanning calorimetry was employed to describe the δ-form of chloramphenicol palmitate and to study its interconversion to other forms (819).

The physical properties of 20% gelatin gels prepared from Pharmagel A were investigated, and their behavior in electric fields was explored (820). A review of the literature dealing with the modification of crystalline structures of pharmaceutical solids and its application was published (821). The effect of various additives on the rate of transformation of metastable anhydrous succinylsulfathiazole Form I to the water-stable dihydrate Form II in aqueous suspension was reported (822, 823). Structurally related compounds, viscosity-imparting agents, surfactants, and colorants were used as possible retardants for the conversion. Methylcellulose, phthalylsulfathiazole, and polysorbate 80 were shown

to inhibit crystal growth of suspensions prepared from the metastable polymorph. Physical factors and additives that had accelerating or retarding effects on the transformation rate of Form I had similar effects on the crystal growth rate in aqueous suspension.

A review of the pharmaceutical aspects of crystallography was presented (824).

Electron microscopy was employed to determine the physical properties of dextran and polyvinyl alcohol in solutions (825). Formation of aggregates and the effect of time and concentration on aggregation were described. The relationship between the polymer structure and biocompatibility of hydrophilic gels was investigated (826). A method for preparing microcrystals of aspirin by pouring a hot solution with glycol into cold water was presented (827), and no evidence of polymorphism was found.

An X-ray diffraction method was employed to study the apparent velocity constant of the degradation of the crystalline network of an aspirin–aminophenazone (aminopyrine) mixture (828). Starch apparently retarded the decomposition. The kinetics of particle-size reduction was followed by investigating the time dependence of the average size (829). The physical properties of mixtures of oleic acid with tripalmitin and with fatty acid triglycerides were studied (830). Oleic acid appeared to retard the release of salicylic acid from a suppository formed from fatty acid triglycerides.

The role of principal component analysis in the selection of pharmaceutical formulations was discussed (831). The technique was successfully applied to a system consisting of 10 tablet variables. This methodology may be useful for achieving cost and time savings in measuring responses. A simple test was made to determine the importance of surfactants in the disintegration of tablets (832). The determining factors appeared to be the hydration of the bonding agent and the dissolution of binding bridges. The pK values for about 600 drugs were presented, and the importance of the dissociation constant and lipid solubility in determining the potential drug activity was discussed (833–835).

The uses and medical applications of polymer membranes and silicones were reviewed. Special emphasis was paid to medical grade silicone (836, 837). Size distribution of particles in solutions, suspensions, and ointments was studied using optical electronic imaging evaluation (838). The limitations of the method and the reproducibility of the results were discussed. Reviews of the physical properties, stability, and analysis of phenformin hydrochloride, norgestrel, norethindrone, and cephalexin were published (839–842).

Dissolution—A general equation was derived for the dissolution profile of powders under sink conditions (843), was used to develop an equation for the dissolution of log-normal powders, and was found to be more applicable than previous approaches. A biphasic cube-root dependence was found in the dissolution of oxalic acid dihydrate of log-normal particle-size distribution in 0.1 *N* HCl (844).

Dissolution profiles were calculated for sieve cuts of varying widths on the assumption of diffusion rate-limited dissolution under sink conditions from spherical particles (845). Even narrow sieve cuts varied from cube-root law expectations by as much as 3%, but the experimental data could be treated on the assumption that sieve cuts act like monosized powders to provide acceptable information, except in cases of critical tests of dissolution rate theory. Equations describing nonsink dissolution rates on the basis of simple film theory were shown to hold to 80–90% of the dissolution process for *p*-hydroxybenzoic acid and sodium chloride (846).

A critical review of drug dissolution focused upon methods for determining rates that could lead to realistic specification standards (847). A mathematical model based upon convective diffusion was developed to describe the rate of dissolution from the surface of a compressed compact (848, 849). Correlations between experimental results and theory were good for describing dissolution rates from rectangular and circular surfaces of a homologous series of *p*-aminobenzoate esters.

Dissolution rates of three polymorphs and two hydrates of phenobarbital were determined, and Form II dissolved most rapidly (850). On the basis of dissolution studies of chloramphenicol palmitate polymorphs in pancreatic solutions, it was determined that the first step of enzymatic hydrolysis could not be drug dissolution but rather appeared to be ester hydrolysis in the undissolved state (851). Linear multiple-regression analysis was used to assess the dependence of the dissolution rate on the diffusion coefficient and viscosity of the dissolution medium (852).

Dissolution profiles of aspirin from three dosage forms (microcapsule, powder, and enteric-coated granule) were examined at constant pH (853). The dissolution process of microencapsulated drug was zero order in the initial phase of the experiment. An irregularly shaped dissolution pattern was obtained with the enteric-coated granules. FD&C Violet No. 1 and Ext D&C Blue No. 1, at 50 μg/ml, inhibited the dissolution rate of sulfathiazole, diethylstilbestrol, and hexestrol in micellar bile solutions (854). The effect of the dissolution rates of drug solid dispersion systems on the GI absorption of drugs was reviewed (855). A model system, using a rotary disk technique, was developed to measure the dissolution rate and change of testosterone to testosterone monohydrate II (856).

Solid dispersions of several steroids, hydrochlorothiazide, and phenylbutazone in povidone (PVP) or polyethylene glycol 6000 exhibited more rapid dissolution than optimally wetted and dispersed pure drug powders (857). Formation of solid dispersions of indomethacin, however, did not increase the dissolution rate. Ball milling in the presence of povidone increased the solubility and dissolution rate of phenothiazine, vitamin K_3 (menadione), and other insoluble drugs (858). Low concentrations of povidone decreased the apparent solubility of hydroflumethiazide, whereas solubility was enhanced at high concentrations (859). Dissolution data were consistent with a model accounting for crystalline and amorphous drug together with complexing and crystal growth-inhibiting effects of povidone. The enhancing effect of povidone upon tolbutamide solubility was suggested to result from complex formation as demonstrated by TLC and IR measurements (860).

Stirring frequency had a greater effect upon the dissolution rate than did stirrer positioning in a study of factors affecting dissolution rates of benzoic acid from flat-faced disks (861). A system employing continuous extractions of drugs from the aqueous medium in a closed system was employed to determine the dissolution rate of slightly soluble drugs (862). The Sartorius solubility simulator was superior to the rotating-basket method and the disintegration apparatus method for determining dissolution rates of drugs from solid dosage forms (863).

An adaptation of the Langenbucher continuous-flow apparatus was used to determine dissolution rates of prednisolone tablets (864). The beaker and column methods for determining drug dissolution gave more reproducible results than the rotating-basket method in dissolution testing of acetaminophen (865). An automated dissolution test apparatus was proposed and evaluated with diazepam, methyldopa, phenylbutazone, and oxytetracycline tablets (866). A highly versatile, reliable, automated *in vitro* dissolution test apparatus for pharmaceutical solids, using a rotating filter–stationary basket was described (867). Tablet dissolution rates were determined with a relative standard deviation of 1.09 *versus* 16.6% with an automated USP–NF method.

A multichannel, continuous-flow apparatus for dissolution rate measurements was described (868). Typical data were presented to demonstrate its utility for drug powders as well as tablets and capsules. Column flow-through methods for tablet dissolution rate determinations were reviewed, and their superiority to beaker methods was suggested (869).

As in previous years, the assessment of digoxin dissolution from tablet dosage forms received attention. Single-tablet dissolution studies were performed with digoxin using the USP rotating-basket assembly (870, 871). Dissolution profiles for 11 samples of digoxin tablets revealed variations between samples from different manufacturers, different batches from a single manufacturer, and single tablets from a single batch. Samples from 105 production batches of digoxin tablets, produced in the United Kingdom, had 12-hr dissolution ranges of 43–100% of labeled strength (872). In another study, dissolution rates correlated closely with plasma levels found in the first 7 hr after an oral dose (873). It was suggested that the differences in dissolution rates between different brands is an important determinant of biological availability and that the measurement of the digoxin dissolution rate after 1 hr is a useful guide for assessing bioavailability.

Dissolution studies of enteric-coated tablets and granules of aspirin were performed using the USP rotating-flask method and the beaker method (874). Good correlation was shown between *in vivo* absorption with dissolution rates obtained with the rotating-flask procedure. Another study showed that for aspirin only the rotating-flask method at 50 rpm gave statistically correlatable results with *in vivo* data when 10-min dissolution rates were compared to 1-hr urinary excretion values (875). Several brands of enteric-coated sodium salicylate tablets were evaluated for *in vitro* dissolution characteristics and plasma levels (876). Although most tablets provided full availability, absorption rates were highly variable.

Table XXI—Additional References on Dissolution

Reference	Topic
886	Effect of aging on dissolution of phenylbutazone tablets
887	Eutectic mixtures of aspirin and urea
888	Size distribution effects in multiparticulate dissolution
889	Concept of dissolution efficiency
890	Transition temperature and heat of transition of barbital polymorphs
891	Transition temperatures of sulfanilamide polymorphs determined by dissolution rate measurements
892	Influence of processing and bile salts on the dissolution rate of flufenamic acid tablets
893	Review of dissolution rate of powders
894	Dissolution of aspirin–polyethylene glycol 6000 coprecipitates
895	Dissolution of acetaminophen solidified melts
896	Parameters in dissolution rate studies
897	Tablet dissolution apparatus
898	Variability in automated dissolution determinations
899	Disintegration and dissolution of tablets
900	Dissolution of propyromazine from directly compressed tablets
901	*In vitro* dissolution of digoxin from tablets
902	Dissolution testing of L-dopa (levodopa) tablets
903	Dissolution testing of glutathione tablets
904	Dissolution of caffeine and salicylamide tablets
905	Differences in USP disintegration test and *in vivo* behavior of enteric-coated tablets
906	Dissolution and stability of silicone-coated ascorbic acid tablets
907	Comparison of tablet dissolution and disintegration rates
908	Review of solubilization techniques
909	Solubilities of barbiturate polymorphs

The effect of hardness on disintegration and dissolution characteristics of uncoated caffeine tablets made at eight different pressure levels were studied (877). Tablet hardness affects dissolution from the tablets as well as from fully disintegrated granules and small particles. A continuous-flow column apparatus was used to study the dissolution rate of sulfamerazine sodium and was recommended for distinguishing between tablets of varying composition and for assessing batch-to-batch variation (878). A comparative study of the *in vitro* release of three brands of slow-release potassium chloride tablets was presented, and the data were critically examined in the light of dissolution rate equations (879). The time required for 50% dissolution of five brands of tetracycline capsules varied from 4.6 to 30.5 min under standardized conditions at pH 1.4 (880).

An apparatus utilizing liquid turbulence to simulate hydrodynamic conditions generated by GI peristalsis was designed to estimate drug release from solid oral dosage forms (881). A correlation was developed between dissolution rates and absorption patterns of two misformulated tablets. Great variation was observed in dissolution rates of 15 brands of quinidine sulfate capsules and tablets (882). The rank order of dissolution in 0.1 *N* HCl and in phosphate buffer was not the same. The release rates of quinine sulfate from time-released tablets prepared with various amounts of carbomer

934P and cellulose acetate phthalate at different compaction pressures were measured (883). Dissolution rates of commercially available chlorothiazide and hydrochlorothiazide tablets were determined (884). The time required for 100% dissolution was less than or equal to 100 min for all samples except one, which had a value of 190 min. Although differences in *in vitro* dissolution between anhydrous ampicillin and the trihydrate were recorded, *in vivo* availability of the two substances as determined from loosely filled hard gelatin capsules was the same (885).

Additional references on dissolution are listed in Table XXI.

Solubility–Solubilization Phenomena—A physical model approach was utilized to study cholesterol gallstone dissolution in simulated bile (910). Quaternary amines enhanced dissolution rates of gallstones in bile acid–lecithin solutions; in bile acid systems, cholesterol dissolution was sensitive to electrolyte concentrations (911). Sodium chloride increased cholesterol dissolution rates in sodium cholate solutions. In another study, various drug compounds excreted in bile were evaluated to determine their potential for increasing the solubility of cholesterol in bile (912). A viable *in vitro* screening method for identifying compounds that enhance biliary-holding capacity for cholesterol was proposed.

The pH–solubility profiles of tetracycline antibiotics in hydrochloric acid–sodium acetate buffer solutions were obtained at 37° (913). Chlortetracycline had a maximum solubility at pH 2.8, whereas tetracycline, demethylchlortetracycline (demeclocycline), and methacycline showed increases in solubility with decreasing pH. The solubility of oxytetracycline in double-distilled water at pH 6.5 and 20° was reported to be 195 μg/ml (914). Substituted ureas were studied for their solubilizing effect upon aminophenazone (aminopyrine), caffeine, sulfanilamide, and *N*-acetylsulfanilamide. In all cases, thiourea enhanced the solubility to a greater extent than urea did (915). Short chain aliphatic amine hydrochlorides were reported to depress the solubility of benzoic acid, aminophenazone, and caffeine in water (916). The effect decreased with increasing chain length. A study of the uptake of halothane and trichloroethylene in aqueous dispersions showed that coagulated systems appeared to absorb more vapor than did flocculated structures (917).

The aqueous solubility of steroids increased exponentially following the addition of a cosolvent (918). An equation was derived to describe the relationship between the amount of drug solubilized and the volume fraction of cosolvent incorporated. Both single and multiple cosolvent systems followed the derived relationship. Neglect of steroid absorption onto membrane or fiber filters was reported to be responsible for erroneous solubility values reported in the literature (919). This problem was uncovered in a solubility study which demonstrated the increase in solubility of estradiol in the presence of progesterone. Amino acid prodrugs of acetaminophen provided water-soluble forms of the drug (920). Although the lability of these esters precluded their use in liquid dosage forms, their use in solid products was recommended. The solubilization of water and water–amide solutions by bis(2-ethylhexyl) sodium sulfosuccinate in heptane was studied (921). A linear relationship was shown between moles of water solubilized per mole of surfactant and the surfactant concentration.

A mixed polysorbate–sorbitan surfactant system was employed to solubilize liquid paraffin (922). Incorporation of the solubilizate within the nonpolar environment created by the combined hydrophobic portions of the mixed surfactants was proposed as a possible mechanism. The influence of surfactant structure on, and distribution of salicylic acid in, micelles was reported (923); structurally related polysorbate and polyoxyl[14] surfactants were employed.

Spray-drying techniques were used to improve the solubility and dissolution rate of salicylic acid (924). Spray drying from acacia solutions resulted in as much as a 50% increase in solubility, and the dissolution rate was about 60 times faster than that of the drug alone. A study of the solubility of caffeine and aminophenazone (aminopyrine) in the presence of sodium salts of organic carboxylic acids showed that the solubility increased with increasing acid chain length (925). Determination of solubility of actinomycin D (dactinomycin) revealed that the solubility increased with a decrease in temperature (926). By a freeze-thaw technique, aqueous concentrations as high as 0.5 mg/ml were obtained at room temperature.

A study of the effect of pH, temperature, and electrolyte concentration on the solubilization of phenobarbital and barbital in nonionic surfactants showed that the degree of interaction increased as the temperature increased (927). This result was attributed to the improved solubility of the barbiturate in the micelles and not to alteration of the micellar structure. Alkyl esters of *p*-aminobenzoic acid were solubilized by lysophosphatidal choline (928). Solubilization increased in the following order: ethyl, *n*-propyl, and *n*-butyl esters. Sodium escinate dissolved more rapidly in artificial gastric juice than did amorphous escin (929). A literature review of the effect of compounds in enhancing riboflavin solubility in water and the mechanism of solubilization was provided (930).

Membrane Permeation and Release—Relative permeation constants for phenobarbital, salicylic acid, and nitrazepam through hexadecane–collodion membranes were determined (931). An equation independent of membrane area and volume of compartments was developed to describe drug permeation through artificial lipid membranes. Zero-order release kinetics were obtained when a film without drugs was laminated to the releasing side of a film containing dispersed drug (932). In this manner, the drug layer served as a reservoir to control the duration of drug release while the nondrug layer determined the rate of permeation. Hydroxypropyl cellulose was employed as the reservoir layer, and mixtures of hydroxypropyl cellulose and polyvinyl acetate were used as the inert layer. Inverse relationships between the release rate and membrane thickness and between the logarithm of the rate and the percentage of polyvinyl acetate in the membrane layer were observed.

[14] Myrj, ICI United States.

Dissolution rate studies of quinine sulfate from polyamide matrixes in simulated gastric and intestinal juice in the presence of surfactants revealed that the dissolution rate was dependent upon dissolution medium pH and the type and concentration of the surfactant employed (933). Pinhole-free silicone membranes were produced by removal of silica filler aggregates prior to casting of the dispersion (934, 935). A procedure for the preparation of fabric-reinforced membranes was also developed. Postcuring membranes with UV irradiation increased tensile strength by 30%. These defect-free membranes were more biocompatible than commercially available membranes.

Membranes consisting of the polyvinyl alcohol and oxystarch were described (936, 937). A cross-linking structure within the membranes was suggested, and the relationship between permeability and preparation conditions was studied. Lecithin–collodion membranes were employed to determine the permeability of various drugs (938, 939). A correlation was exhibited between membrane permeation and absorption from the GI tract. However, a direct relationship could not be established between membrane permeation and partition coefficients in octanol–water. The membrane permeability for lipid-soluble substances was temperature dependent and decreased when membranes were washed before use or were stored for long periods. The effect of lecithin–collodion ratios upon membrane properties was explored.

The permeability of drugs from ethylcellulose films containing up to 50% polyethylene glycol 4000 was determined (940). For salicylic acid and caffeine, steady-state constants were independent of film thickness and solute concentration but increased linearly and sharply with polyethylene glycol content. Mass transfer appeared to be controlled by a solubility diffusion process in the ethylcellulose of the membrane. Enhancement of permeability by polyethylene glycol appeared to be due to increased membrane porosity. Balancing of membrane porosity and thickness could be employed to control drug release. A review discussed ophthalmic applications of membrane-controlled drug delivery systems (941).

Low concentrations of dioctyl sodium sulfosuccinate increased the rate of pentobarbital absorption from the rat small intestine (942). Higher concentrations decreased drug penetration due to micellar effects.

A general equation was proposed to predict the diffusion coefficient of a drug in a polymeric gel from the molecular weight, the diffusion coefficient of the compound in solvent, and the polymer concentration of the gel (943). A logarithmic dependence of the diffusion coefficient on polymer concentration and solute molecular weight was observed in a study of the release of hormonal implants in hamsters. Membranes prepared by casting thin films of polyalkylsulfones onto porous polypropylene provided greater oxygen and carbon dioxide permeation than did silicone membranes (944). The potential application of these films for drug implants was suggested.

A homologous series of quaternary esters of benzilic acid was employed to study the partition behavior in a three-phase water–1-octanol–water system. The rate-determining step for interphase transport of hydrophilic compounds was diffusion through the organic layer (945). The rate constants for transfer from the aqueous to the organic phase increased linearly with the corresponding partition coefficient. As the chain length increased, diffusion through the aqueous diffusion layer became rate determining; thus, rate constants were independent of partition coefficients. The relationship of these studies to biological considerations was discussed.

An *in vitro* test apparatus was developed to measure release of ionic drugs from ointment bases (946), and the release of sodium salicylate from a petrolatum ointment base was studied using this apparatus. The permeation constants for a group of structurally related homologous heterocyclic compounds through lecithin membranes were directly related to their decanol–water partition coefficients (947). The effect of serum and membrane binding and intrinsic membrane permeability upon the uptake and release kinetics of drugs in living systems was studied using three cardiac glycosides in the Burkitt lymphoma cell system (948). The data conformed to a physical model of rapid solute equilibration within the cell after permeation through the rate-determining plasma membrane barrier. Transport of digitoxin was influenced by membrane and serum binding, while transport of digoxin was influenced by membrane binding only.

Increased rates of permeation of sulfaguanidine through the intestinal lumen of rats occurred when the drug was coadministered with chelating agents and surfactants (949). Except for poloxamer 188[15], all additives produced histological changes. It was suggested that changes in the rate of permeation with time be used as an indicator for the damaging effect of drugs on the intestinal mucosa.

A two-compartment diffusion cell employing a semipermeable cellophane membrane was used to determine diffusion rates of tetracycline at various pH values in the presence of metal ions (950). Tetracycline chelate formation was pH dependent. Chelation reduced diffusion even where water-soluble chelates were formed. Anomalies in the phase transfer of phenylbutazone were attributed to unusually slow protonation and deprotonation reactions (951). General physical models were derived for the diffusional transport of drugs across membranes of mammalian cells (952). The models were developed to represent different sets of possible physical processes that take place during drug transport. In these models, the assumption was made that the cell membrane is an integral part of the total barrier. This model was used to explain the kinetics of uptake and release of desmosterol, cholesterol, and β-sitosterol by Burkitt lymphoma cells (953). Effects of permeability and partition coefficients of the sterols were inversely proportional to the serum concentration in the external medium due to sterol–serum binding. The results were consistent with the mechanism in which only unbound solute participates in the membrane transport process.

The absorption of benorilate across the everted rat

[15] Pluronic F-68, Wyandotte.

intestine showed that the physicochemical form in which the drug was present was the primary factor in determining the rate of passage (954). The entry of intact drug into mucosal cells appeared to be the rate-determining step in the absorption process. Drug hydrolysis occurred during passage through the intestinal wall. An *in vitro* apparatus was employed to evaluate factors affecting the membrane permeation of dihydroergotoxin methanesulfonate, and the absorption rate from the small intestine was predicted (955). Carbomer 934P[16] was shown to delay membrane transport.

Incorporation of water, dimethyl sulfoxide, and alcohol at 1–5% concentrations accelerated the rate of release of atropine sulfate from various ointment bases as determined by an *in vitro* study (956). The diffusion of drug was zero order during the initial phase of the release. Procedures were developed for studying the release of fluocinonide and flucloronide from oleaginous ointment bases containing various adjuvants (957). Data obtained from model systems enabled rates from modified ointment bases to be predicted. The simple model did not provide correlation for ointments containing emulsifying agents.

The effects of interaction between drug and skin, drug and vehicle, and vehicle and skin on the penetration rate of a drug through the skin were evaluated by comparing penetration rates through excised skin and polyethylene (958). Dimethyl sulfoxide, dimethylformamide, ethanol, and water increased permeability of the skin, but they reduced penetration through the polyethylene membrane. Release rates of 8-hydroxyquinoline sulfate from hydrophilic and hydrophobic vehicles were determined (959). Release from aqueous vehicles was faster than from lipophilic preparations. Ointments containing zinc oxide prevented drug release.

Solubilization of chloramphenicol with dimethylacetamide resulted in markedly accelerated release rates of the drug from petrolatum vehicles (960). A study of the release of prednisolone from an oil-in-water emulsion showed that increasing the drug concentration by a factor of 4 resulted in an increased liberation rate of only 1.6 from the base (961). These results were supported by clinical findings. Release of hydrocortisone from a propylene glycol–alcohol–water gel did not agree with theory based upon Poulsen's hypothesis (962), but release of cortisone from similar gel systems conformed to this theory.

A mathematical model of the stratum corneum was proposed in which the tissue was described as a two-phase protein–lipid heterogeneous membrane with the lipid phase being continuous (963). In this model, the permeability of the membrane was correlated with the water solubility of the penetrants and with their lipid–protein partition coefficient. Experimentally measured permeabilities of human skin to various drugs conformed to the model. In another study, mathematical models were developed to simulate percutaneous drug absorption and drug transport within an ointment (964, 965). Ointment and skin were assumed to be homogeneous phases through which drug diffuses according to Fick's law. The percutaneous absorption of sodium iodide from the hydrophilic ointment agreed with calculations based upon the developed model. The effect of the ointment vehicle upon penetration of nicotinic acid and its esters into skin was studied (966). Water appeared to be the most suitable vehicle, whereas propylene glycol and olive oil were less satisfactory. Nicotinic acid penetrated skin more slowly than did the esters from all vehicles studied.

An apparatus consisting of a Lucite cell divided into two compartments by a clamped rabbit cornea was devised for studying formulation effects on drug transport through the cornea, and the reliability of the system was tested (967). The Resomat, an apparatus for *in vitro* absorption studies, was evaluated for correlation with *in vivo* results (968). Reproducible results were obtained when the same batch of membranes was employed, and absorption profiles for drugs gave good agreement with usual theories of drug absorption *in vivo*.

Additional references on membrane permeation and release are listed in Table XXII.

Table XXII—Additional References on Membrane Permeation and Release

Reference	Topic
969	*In vitro* transport of tetracyclines through everted rat intestine
970	*In vitro* release of vitamin A from ointment bases
971	Diffusion of ethylparaben in polyethylene glycol ointment
972	*In vitro* release of chloramphenicol from suppository bases
973	*In situ* transport of flavonoids across rat small intestines
974	Permeation of antidepressants and phenothiazines through cellulose membranes
975	Diffusion of penicillin G and ampicillin through phospholipid sols
976	Synthetic semipermeable membranes for biomedical processes
977	Review of use of membranes in pharmaceutical research
978	Biological fuel cell incorporating selective membranes
979	Mathematical analysis of membranes; solution–solubility dependency of controlled-release drugs from polymer matrixes
980	Controlled drug release from matrix systems
981	Penetration of water vapor through lipid monolayers
982	Effect of chemical modifications on transmembrane permeation in rats
983	Effect of tubular secretion inhibitor on organic anion transport
984	Release of resorcinol from ointment vehicles
985	Development of *in situ* vaginal drug absorption procedure
986	Method for studying release from ointment bases
987	Effect of experimental conditions on *in vitro* release from ointments
988	Transepidermal penetration of venoruton (troxerutin)
989	Effect of polyethylene glycol 300 on release of hydrocortisone from ointments

Complexation—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—An ultrafiltration procedure was employed to demon-

[16] Carbopol 934, Goodrich.

strate that, at a 20-μmole level, more than 98% of furosemide was bound to a 7.5% albumin solution (990). Studies with an isolated perfused rat kidney showed that albumin inhibited tubular clearance of the drug. Binding of thiopental to plasma proteins from healthy, cirrhotic, and uremic subjects, using equilibrium dialysis, showed that the greatest binding occurred in the healthy subjects (991). In human blood plasma, digitoxin, digoxin, and other cardiac glycosides were extensively bound to plasma proteins (992). One mole of glycoside appeared to bind per mole of albumin.

A fluorescence assay procedure was employed to study the displacement of warfarin from human serum albumin by other drugs (993). Dicumarol, phenylbutazone, rifampicin (rifampin), ethacrynic acid, tolbutamide, and salicylic acid displaced warfarin (in decreasing order). In the therapeutic range, about 35% of the serum morphine concentration was bound to human plasma, primarily to the albumin fraction, as shown by equilibrium dialysis experiments (994). The binding of furosemide to human albumin was studied by dialysis (995). Decreased binding occurred in the presence of aspirin, diazoxide, phenylbutazone, and sulfisoxazole. The interaction of phenothiazine and aminodibenzyl compounds with human serum albumin was demonstrated by spectrofluorometric quenching titration (996). Competition for binding sites and binding constants were determined.

Under *in vitro* conditions, six anticonvulsants and aspirin did not significantly displace carbamazepine from plasma protein binding sites (997). *In vivo* studies showed that only about 27% of the drug was unbound in serum. The stoichiometry and strength of binding of pamaquine to bovine serum albumin were monitored by a fluorometric technique (998). The results indicated that three singly protonated pamaquine molecules were bound per mole of albumin. Binding constants were calculated using the Bjerrum procedure.

The relationships among protein binding, distribution, and kinetics of elimination of warfarin were studied (999). The results showed excellent correlation between the fraction of free drug in rat plasma and the plasma clearance of the drug. Large intersubject variation in fraction bound was not related to variations in serum albumin or total protein concentration. These differences may reflect individual configuration differences of proteins or the presence of an endogenous displacing agent at different concentrations. Benzalkonium chloride reduced sulfaethidole binding to bovine serum albumin (1000). The concentration of ethambutol in human cerebrospinal fluid was a function of the nonprotein-bound drug fraction in serum (1001). Serum protein binding varied from 8.3 to 39.3%, depending upon serum level.

The elimination rate of bilirubin was reported to be proportional to the concentration of free bilirubin in plasma (1002). Protein binding decreased the excretion rate. The importance of using specific analytical procedures for a drug in the presence of its degradation products or metabolites was demonstrated during protein binding studies with warfarin, since anomalous results were obtained when nondiscriminatory procedures were employed (1003).

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

Reference	Topic
1013	Serum binding of digoxin
1014	Model for modified drug absorption; effect of surfactant on chloramphenicol binding to an albumin–lecithin complex
1015	Effect of divalent cations on adsorption of prothrombin complex
1016	Stereospecific binding of D-lysergic acid diethylamide (lysergide) to brain membranes
1017	Binding site interaction of chlorthalidone and acetazolamide to red blood cells
1018	Binding of chlorpromazine and imipramine to blood components
1019	Binding site interaction of chlorthalidone and acetazolamide
1020	New fluorescence probes for drug–protein binding studies
1021	*In vitro* binding of bromophenol blue and amaranth to liver cytoplasmic binding proteins
1022	Decreased plasma protein binding to diazoxide in uremia
1023	Morphine and phenytoin binding to plasma proteins in renal and hepatic failure

The use of kanamycin to inhibit bacterial growth during plasma binding studies was recommended, since this agent did not appear to bind nor to interfere with the binding of other compounds under investigation (1004).

Quinidine was shown to bind at two sites on serum albumin (1005). Computations showed that 74–88% of the administered drug would be bound to albumin and that 71–74% of this fraction would be bound by the high affinity sites on the protein. Quantitative relationships between therapeutic levels of quinidine and its distribution in plasma were discussed.

Gelatin–acacia coacervate systems were employed as models for protein binding studies of drugs (1006). The protein binding characteristics of chloramphenicol and several other antimicrobial agents were described using this procedure. The fraction of methaqualone bound to human serum was determined, by equilibrium dialysis, to be 80% in the therapeutic range (1007). The drug concentration in cerebrospinal fluid correlated well with unbound drug levels in serum. The extent of plasma binding of 13 disopyramide derivatives was reported (1008). Structural variations influenced binding characteristics, with a linear correlation being exhibited between binding and drug lipophilicity.

Metronidazole and four derivatives were studied *in vitro* to determine the effect of structural differences upon binding to plasma proteins (1009). A linear correlation was found between the protein binding parameter and the frontier electron density on the hetero atom at the 3′-position on the alkyl side chain, as shown by NMR techniques. The administration of phenylbutazone together with warfarin to dogs produced an elevation of the free fraction of warfarin in plasma, with a resultant twofold decrease in the plasma half-life of the drug (1010). The antimicrobial activity of sulfadimethoxine in rabbit plasma was significantly increased by concomitant injection of phenylbutazone (1011). The binding of papaverine to plasma components of several animals was investigated to show that binding occurred in all species to an extent greater than 90% at physio-

logically active levels (1012).

Additional references on the interactions of drugs with biological substances are listed in Table XXIII.

Interactions of Drugs with Nonbiological Substances—A permeation rate technique was employed to study the interaction of methylparaben with polyvinylpyrrolidone (povidone) and polysorbate 80 (1024). The results obtained were in agreement with data reported by other techniques, and it was concluded that dynamic dialysis could be used to quantitate drug binding by macromolecules. The self-association of antihistaminic drugs was investigated by light scattering (1025). A CMC could not be detected. For a number of the compounds, the data were consistent with the model involving aggregate growth by the stepwise addition of monomers.

A study of the interactions of α-cyclodextrin and β-cyclodextrin with nonsteroidal anti-inflammatory drugs showed that β-cyclodextrin accelerated the degradation of azapropazone (apazone) but retarded the decomposition of phenylbutazone (1026). Addition of urea to the solution promoted inclusion of the drug within the β-cyclodextrin, while sodium chloride gave the opposite effect. A 1:1 stoichiometric ratio was found to exist for the complexes formed between β-cyclodextrin and fenamates, *trans*-cinnamic acid, or phenothiazines (1027–1029). Complex formation was studied using circular dichroism, UV absorption, and NMR spectroscopy. The binding mechanisms and the positioning of the small molecules within the β-cyclodextrin were postulated from the results. On the basis of IR spectral data, complex formation between barbiturates and polyethylene glycol 4000 was shown to occur through hydrogen bonding between the nitrogen hydrogens of the barbiturate ring and two oxygen atoms of the polyoxyethylene moiety (1030). The aqueous stability of these complexes as a function of varying barbiturate structure was discussed. A literature review described the interaction of iodine with solvents and surfactants (1031).

Differential thermal analysis was employed to determine the stoichiometry of complexes formed between aspirin and phenobarbital, chloramphenicol and methenamine, and other drug systems (1032). The effect of complexation with caffeine on the *in vitro* transport of salicylates was studied using a three-phase liquid barrier model (1033). Generally, the presence of caffeine decreased salicylate transport. By using a similar system, only slight retardation of chlorpromazine transport through a lipoidal barrier was observed in the presence of various xanthines (1034). On the other hand, the rate of chlorpromazine diffusion through a dimethicone[17] membrane in the presence of complexing agents was markedly decreased.

The types and structures of inclusion compounds of pharmaceutical importance were reviewed (1035). Solubility profiles for benzocaine–caffeine, menadione–desoxycholic acid, and other systems were obtained in mixed solvents of ethanol–water and propylene glycol–water (1036); the interactions were affected by the composition of the solvents. Menadione photodegradation was inhibited in the presence of solutions of cetylethylmorpholinium ethosulfate (1037). Complexation in this system was demonstrated by shifts in the UV absorption spectrum.

Evidence was presented for the formation of a phenobarbital–ephedrine complex in the solid state, and the physical properties of the complex were elucidated (1038). Coprecipitates of tolbutamide with povidone and fusion mixtures with polyethylene glycol 6000 were evaluated for dissolution rate enhancement (1039). Complexation was shown to occur between tolbutamide and povidone, but no binding could be detected with polyethylene glycol 6000. Complexation between menadione and hydrotropic salts was evaluated by solubility analysis (1040). Spectral studies indicated that molecular interactions occurred at low concentrations, whereas the hydrotropic effect predominated at high salt concentrations.

Anionic drugs such as benzoic acid and salicylic acid were shown to bind by ion exchange to hydroxyl groups on the amphoteric surface of titanium dioxide below pH 6.5, whereas cationic drugs bound to titanium dioxide

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

Reference	Topic
1045	Interaction of antipyrine and caffeine with sulfacetamide
1046	Review of principles of preservative inactivation by nonionic surfactants
1047	Dissolution and physical properties of the *p*-aminobenzoic acid–caffeine complex
1048	Inhibition of hydrolysis of acronycine (acronine) esters by complexation
1049	Interaction of sodium citrate with bivalent metal ions
1050	Binding of cationic drugs by carboxymethylcellulose
1051	Interaction of methylparaben with polysorbate surfactants determined by solubility studies
1052	Metal complexes of anhydrotetracycline
1053	Influence of cosolvents and substrate substituents on sorption of benzoic acid derivatives by polyamides
1054	Acetaminophen binding by a biocompatible polymer-coated charcoal
1055	Interaction between cortisone and arginine
1056	Interaction of vinyl acetate–vinylpyrrolidone copolymer with surfactants
1057	Interaction of sodium dodecyl (lauryl) sulfate with monoalkylolamides of aliphatic acids
1058	Determination of interactions between hydrocarbons and polyoxyethylene nonylphenyl ethers by GC
1059	Interaction of polyvinyl alcohol with benzoic acid and its monohydroxy derivatives
1060	Binding of quaternary surfactants by carboxymethylcellulose
1061	Interaction of sorbic acid and emulsifiers
1062	Interaction of a cationic substituted cellulose ether (Polymer JR) with surfactants
1063	Interactions of polyethylene glycol 6000 and povidone 40,000 with succinylsulfathiazole and chlorpropamide
1064	Properties of interaction products between ethyl gallate and surfactants
1065	Review of release of pharmaceuticals from macromolecular hydrophilic complexes
1066	Review of interactions between surface-active agents and polymers
1067	Distribution and antimicrobial activity of preservatives in solubilized and emulsified systems

[17] Silastic, Dow-Corning.

at alkaline pH values (1041). On the basis of X-ray diffraction measurements, the conclusion was reached that codeine cations bind to montmorillonite clays between the silicate layers (1042). The reaction was shown to depend upon the particle size and charge distribution of the clay as well as on the pH and ion concentration of the medium.

Complexation between morphine and divalent cations was demonstrated by spectrophotofluorometric analysis (1043). The fluorescence intensity of the magnesium complex was depressed in the presence of calcium. Formation constants for the interaction of iron(II) ions with ascorbate, fumarate, and succinate ligands were determined, and the results were employed in a computer model to predict absorption from the small intestine (1044). It was predicted that optimum absorption would occur with ligands having a divalent anionic charge that formed 1:1 complexes. The model also allowed for low molecular weight polymers.

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

Surface Phenomena—The publications dealing with surface phenomena are divided into five major categories: (*a*) interface studies, (*b*) adsorption studies, (*c*) general properties of surfactants, (*d*) micelle studies, and (*e*) dispersion stabilization and rheology.

Because of overlap of subject material, the reader with special interest in this field should review the entire section.

Interface Studies—A thermodynamic study of the stability of microemulsions showed that spontaneous formation occurred only when the specific surface free energy was sufficiently small (1068). Phase inversion was predicted, and information on droplet size was derived. An approximate equation based on the average environment of each droplet was used to calculate the entropy of formation.

Light-scattering and depolarization measurements were employed to construct phase diagrams of microemulsion systems (1069). Settling rates for colloidal silicone dioxide dispersed in water and heptane were measured, and the results were interpreted on the basis of an equation for hindered settling (1070). Mean particle radii independent of particle concentration were determined in the system.

The interaction between water vapor and fully hydroxylated surfaces of silicon dioxide, alumina, and aluminum silicate was studied by measuring physisorption isotherms (1071). The strength of sites for physisorption of water increased with the decreasing content of aluminum. Various denture base polymers were evaluated to determine the amount and rate of water uptake (1072). The high diffusion coefficients within certain polymers were indicative of the faster uptake of water and may be related to the amount of cross-linking, the plasticizing effect of the free monomer in those polymers, or to molecular weight. All materials studied took up most of their water during the 1st day, and hydration was essentially complete after 1 week.

A study of the influence of raw materials and manufacturing methods on the surface properties of magnesium silicates showed that the addition of sodium silicate to magnesium compounds produced a silicate having a higher absorption capacity for methylene blue; other physical measurements such as specific surface area, specific gravity, and acidity were the same (1073). The volume of coacervate produced from gelatin–acacia systems varied with the starting and final pH and with the concentrations and ratios of the coacervate materials (1074).

Table XXV—Additional References on Interface Studies

Reference	Topic
1078	Influence of methylene blue and crystal (gentian) violet on emulsifying activity of methylcellulose
1079	Interaction of antihistamines in lecithin monolayers
1080	Factors affecting fibrinogen–fibrin conversion
1081	Surface area measurements by nitrogen and argon adsorption
1082	Review of determination of specific surface area and porosity of solids
1083	Surface activity of antihistamines at air–solution interface
1084	Evaluation of methods for determining antifoam activity
1085	Apparatus for recording change in surface tension with respect to time
1086	Theoretical considerations on mononuclear aggregation of nucleosides in dilute aqueous solutions
1087	Effect of acids and bases on viscosity of salicylic acid–cetrimide system

The wettability of hydroxyethyl methacrylate used for contact lens material was evaluated by sessile drop and captive air bubble techniques (1075). The water content of the gels did not appear to affect wettability in the hydration range investigated. Differences among the gels were most likely due to alterations of surface structure and variations in the methods of preparation. Viscosity, vapor pressure, and electron microscopy techniques were employed to study the molecular characteristics of povidone in solution (1076). It was determined that, with increasing concentration, molecules aggregate to form spheres of increasing size. A study of factors affecting wettability of human skin showed that approaches used to characterize contact angles of low energy solids are of limited value when applied to skin studies (1077).

Additional references on interface studies are listed in Table XXV.

Adsorption Studies—*In vitro* studies showed that uncoated carbon and carbon coated with an acrylic hydrogel were capable of adsorbing drugs from horse serum (1088). Although the polymer coating presented a barrier to the rate of adsorption, it did not affect total capacity. It was suggested that coating with a biocompatible polymer would enable carbon to be used during hemoperfusion in the treatment of drug overdoses. Distribution equilibration was reported to explain the sorption of sulfonamides by neutral, acidic, basic, and quaternary polymethacrylic acid derivatives (1089). Binding occurred primarily by hydrophobic reaction and hydrogen bridging, although ion exchange with the polyions also took place. Because of polymer swelling with increasing pH, maximum binding occurred in the pH region of the isoelectric point of the sulfonamides.

Table XXVI—Additional References on Adsorption Studies

Reference	Topic
1099	Adsorption layer structure during adsorption of nonionic surfactants onto charcoal
1100	Regulating drug binding onto colloidal silica by nonionic surfactants
1101	Adsorption kinetics and interior structure of activated carbon
1102	Adsorption of alkylarylpyridinium chloride by montmorillonite
1103, 1104	Adsorption of sulfanilamides by ion-exchange polymers
1105	Sorption of colored impurities in kanamycin by a cation-exchange resin
1106	Effect of surfactant adsorption on interfacial electrical properties and stability of clay dispersions

The viscosity, sedimentation, and adsorption properties of four aluminum hydroxides employed in the production of bacterial and viral preparations were evaluated (1090). Addition of sucrose prevented loss of stability and sorption properties resulting from freezing and thawing. Sonication produced gels with rapid settling characteristics. Adsorption of orthophosphate onto hydrous aluminum oxide was shown to follow a Langmuir isotherm (1091). Although the sorption capacity was similar to other aluminum oxides, the binding constant was much greater. Urethane-cured crosslinked polybutadiene polymers and polyethylene oxide polymers separately showed little tendency to adsorb bile lipids from micellar solutions (1092). However, polymers containing both types of chains homogeneously distributed were capable of adsorbing large amounts. It was suggested that mixed polymers could be used for regulating cholesterol uptake after oral administration. The kinetics of epinephrine adsorption from aqueous suspensions by fibrous polymeric materials were studied (1093). Complete extraction of the drug into the polymer was achieved by shaking for 15–20 min.

X-Ray diffraction and radioisotope desorption methods provided evidence for the adsorption of povidone onto the surface of montmorillonite (1094). Adsorption of the povidone to the tetrahedral sheets of the polymer was implicated. The adsorption of chlorpheniramine maleate onto kaolin followed a Langmuir isotherm (1095). Lack of discontinuity indicated that only monolayer binding occurred. The adsorption of chlorophyll from benzene solution onto colloidal silicon dioxide followed a stepwise isotherm (1096). This finding suggested the formation of molecular aggregates with increasing concentrations of the pigment in the adsorption layer. Codeine adsorbed onto bentonite or hectorite[18] was shown to be desorbed under physiological conditions of the GI tract (1097). Addition of mucin to the gastric juice increased the desorption. It was suggested that clays could be used in the preparation of oral pharmaceutical products containing cationic drugs. The adsorption of morphine by kaolin was found to obey a Langmuir isotherm (1098). Although washing did not remove the drug from the kaolin, decreased binding was observed in alkaline solutions.

Additional references on adsorption studies are found in Table XXVI.

General Properties of Surfactants—A study was made of the effect of additives on the cloud point of nonionic surfactants (1107). Additives that salted-out polyoxyethylene chains caused decreased stability of oil-in-water emulsions. Additives that salted-in nonionic surfactants increased the effective hydrophilic–lipophilic balance (HLB) of the system.

Nonionic and ionic surfactants had an appreciable effect on the transfer rate of drugs between cyclohexane and water (1108). Increasing concentrations of poloxamer 188[15] increased the rate of phenylbutazone transfer from water to solvent, whereas a decrease in the rate of transfer of alprenolol hydrochloride occurred in the same system.

Changes in the surface tension–concentration curves of cetomacrogol during autoxidation were observed (1109). Decreases in CMC values and cloud points were found. Autoxidation was shown to occur by degradation of the polyoxyethylene chains, with a resultant decrease in CMC values and cloud points. The significance of the findings in relation to the detection of decomposition in synthesized and commercial surfactants was discussed. Mixture of nonionic sucrose-based surfactants and quaternary surfactants produced mixtures having lower CMC values than were found in solutions of the individual surfactants (1110). Multichain nonionic surfactants derived from pentaerythritol were studied for the dependence upon structure of interfacial lowering, foaming, suspending, emulsifying, and detergency properties (1111). An optimum structure for each property was proposed.

Literature reviews were published discussing the use of surfactants in detergent formulations (1112), uses of quaternary ammonium compounds (1113), the synthesis and properties of surfactants (1114), the properties of surfactants in nonaqueous systems (1115), the colloidal behavior of surface-active agents (1116), manufacturing processes and properties of nonionic surfactants (1117), the use of sequestrants in detergent products (1118), and the physical properties of surfactants (1119–1121).

The hydrophobic groups in sodium dodecyl (lauryl) sulfate, ethoxylated dodecanol, and sulfate esters of ethoxylated dodecanol had the controlling effect upon surface activity and micelle formation (1122). The absorption of solids by the surfactants described was examined. Partial phosphorylation of pentaerythritol esters of fatty acids was reported to improve their surfactant properties (1123). The phosphates were found to be good dispersants for inorganic pigments.

The classification of surfactants and applications of the HLB concept were reviewed (1124–1127). HLB values were determined from conductivity measurements of surfactant-stabilized emulsion systems, and an equation was presented for predicting HLB values of a homologous series (1128). A linear relationship existed between the HLB value and the hydrophilic–oleophilic ratio (HOR) for a series of surfactants in water–benzene and water–heptane systems (1129). The

[18] Laporite, Laporte.

Table XXVII—Additional References on General Properties of Surfactants

Reference	Topic
1131	Determination of HLB of fatty alcohol polyoxyethylene ethers by GC
1132	Surface adsorption of *N*-dodecyl-β-alanine in aqueous solution
1133	Colloidal properties of nonionic surfactants in aqueous solution
1134	Interaction of monosubstituted phenols with a cationic surfactant
1135	Review of interactions between surfactants and polymers
1136	Colloidal properties of nonionic and phosphate ester surfactants
1137	Relationship of surfactant structure to efficiency in surface tension reduction
1138	Dependence of properties of mixed block ethylene and propylene oxide copolymers on composition and structure
1139	Determination of hydrophilic and hydrophobic ratios for polysorbate surfactants by proton magnetic resonance and mass spectrometry

minimum HOR values occurred at phase inversion from oil-in-water to water-in-oil emulsions. A thermodynamic definition was provided for the HLB ratio as a function of the chemical potential of a surfactant in the oil and water phases, respectively (1130).

Additional references on the general properties of surfactants are provided in Table XXVII.

Micelle Studies—Ionic equilibria in micellar solutions were discussed on the basis of micelle–monomer equilibrium, mass conservation, and electroneutrality (1140). A decreasing concentration of monomeric form was found to occur as the micellar concentration increased. The structure of lecithin micelles was shown to depend upon the length of apolar portions (1141). Micelle size increased with an increasing concentration of lecithin. CMC's for two-component and multicomponent mixtures of anionic surfactants were determined, and an equation was developed to explain the variation of the CMC with composition on the basis of micellar surface charge and an electrostatic contribution (1142).

The CMC's for the mixed micelles of an alkyl sulfate surfactant and an anionic surfactant were determined and found to be in agreement with theory (1143). Dialysis rates of benzoic acid and its derivatives in aqueous solutions of polysorbate 80 decreased as the surfactant concentration increased (1144). Experimental and theoretical dialysis rates were in good agreement. The dialysis rate constants were inversely related to the lipophilicity of the benzoic acid derivative.

The solubilization ratio of dyes to micelles and their flow dichroism were investigated to determine the mechanism of solubilization (1145). At saturation, one molecule of dye was solubilized per mole of surfactant. At surfactant concentrations above 10%, surfactant molecules were nonspherical and solubilized dyes were oriented within the micelle. The CMC's of surfactants increased with the addition of methyl alcohol to aqueous solutions (1146, 1147). However, when propyl, butyl, or pentyl alcohol was added, a decrease in the CMC occurred. The increasing effect was attributed to a

Table XXVIII—Additional References on Micelle Studies

Reference	Topic
1151	Review of electrokinetic phenomena and micellar structure
1152	Changes in UV absorption spectrum of 1-methylnaphthalene solubilized in micelles
1153	Entropy changes in micelle formation and solubilization
1154	Determination of aggregation numbers and solubilizate diffusion in cationic micelles
1155	Determination of CMC of potassium palmitate by electron spin-resonance spectroscopy
1156	Effect of temperature on CMC of sodium sulfoalkyl esters of aliphatic alcohols
1157	Determination of CMC values of polyoxyethylene glycerol fatty acid ester surfactants
1158	Multiple equilibrium model for micelle formation of ionic surfactants in nonaqueous solvents
1159	Effect of pressure on micelle formation in surfactant aqueous urea solutions
1160	Effect of urea on micelle formation of sodium sulfoalkyl esters of aliphatic alcohols
1161	Effects of inorganic salts and urea on micellar structure of a nonionic surfactant
1162	CMC of multicomponent mixtures of metal alkyl sulfates in solution
1163	Kinetic models for micelle formation
1164	Mechanism of micelle formation in sodium dodecyl (lauryl) sulfate solutions
1165	CMC of sucrose monostearate
1166	Dissociation of fatty acids in micellar systems

weakening of hydrophobic bonds, whereas the decreasing effect was explained by a reduction in the free energy of mixing due to solubilization of the alcohol within the micelle.

Nitrates of cations that form stable solid complexes with model ethers such as dioxane raised the cloud point of nonionic polyoxyethylated surfactants (1148). This increase occurred through salting-in of the surfactants through complexation with the ether oxygens. Nitrates of sodium, potassium, ammonium, and cesium, which do not form complexes with ether oxygens, had the opposite effect. The data demonstrated the need for revising current theories of the effect of salts on the solubility of nonelectrolytes in water, since current theories do not consider the interaction between electrolytes and nonelectrolytes, even though many nonelectrolytes compete with water as ligands for the cations.

Formation of micelles in aqueous solutions by antihistamines (1149) and 2-butyl-3-benzofuranyl-4-[2-(diethylamino)ethoxy]-3,5-diiodophenyl ketone hydrochloride was shown to occur (1150).

Additional references on micelle studies are given in Table XXVIII.

Dispersion Stabilization and Rheology—Addition of an anionic colloidal polyelectrolyte to an antacid suspension resulted in a change in the ζ-potential from positive to negative (1167). Maximum fluidization was confirmed by correlating viscosity measurements with the ζ-potential. Highly concentrated antacid suspensions could be formulated through the use of the procedures described. The physical stability of suspensions and emulsions were reviewed, and the origin and location of charges were related to particulate interaction and electrophoretic mobility (1168). The effect of aging

Table XXIX—Additional References on Dispersion Stabilization and Rheology

Reference	Topic
1178	Effect of size of silica particles on stability of suspensions containing polyethylene oxide
1179	Rheological behavior and effect of aging on soluble salts of cellulose acetate phthalate
1180	Influence of dextran on rheological properties of blood
1181	Relationship of viscosity of celnovocaine solutions to the solution pH
1182	Colloid and surface properties of clay suspensions
1183	Comparison of properties of two grades of tragacanth
1184	Flow properties of gums useful to food industry

at 4° on the viscoelastic properties of acid- and alkaline-processed gelatin gels was investigated (1169). Although a decrease in gel structure due to amide hydrolysis with aging was apparent, viscoelastic properties were not affected. The increased rigidity of alkaline gels was discussed in terms of differences in molecular weight, polydispersity, charge, and charge distribution.

Five petrolatums used in ointment vehicles were tested for rheological properties (1170). Differences in rheological properties were related to the content of cycloparaffins and lower hydrocarbons but not to the isoparaffin fraction. Mechanical treatment decreased the consistency of the petrolatums and petrolatum-containing ointments. The rheological properties of gelatin–glycerin bases were reported to vary with the concentration of components and temperature (1171). The absorption rate of aspirin from rectal suppositories prepared with these bases paralleled the elastic modules. The gelation of 8–30% solutions of gelatin was studied at 24–40° (1172). Transition from a Newtonian liquid to a gel system was detected by a method of deformation at constant shear rate.

Blending of acid and alkaline gelatins was shown to affect rheological properties (1173). Blending reduced rigidity of weak gels, but an increase occurred with stronger gels and more concentrated solutions. The results were explained on the basis of existing charges and intermolecular forces.

Good agreement resulted when apparent viscosity values for pseudoplastic fluids were obtained at the same shear rate on various types of viscometers (1174). Simplified treatment of data from concentric viscometers introduced a systematic error in comparisons with results from cone-plate systems. The magnitude of error increased with increasing ratio between radii of the outer and inner cylinders and with increasing structural viscosity of the solution. The viscosities of carrageenan solutions were compared to those of other commonly employed suspending agents (1175). Carrageenan solutions exhibited significant thixotropy, and an irreversible increase in apparent viscosity occurred at elevated temperature. A calcium carbonate suspension prepared with 0.5% carrageenan showed no sedimentation after 30 days at room temperature.

A concentric core and sphere compression rheometer was designed, and measurements of the rheological characteristics of methylcellulose and carboxymethylcellulose gel systems at low shear rates were obtained with this apparatus (1176). The rheological properties of colloidal silicon dioxide in liquid systems were examined as a function of concentration and the physical and chemical nature of the medium (1177). The colloidal silica exerted greater influence on the viscosity in apolar systems than in semipolar or polar ones. This result was attributed to the possible involvement of secondary valencies in diminishing the interstructure binding forces in the latter systems.

Additional references related to dispersion stabilization and rheology are listed in Table XXIX.

PHARMACEUTICAL ASPECTS

Antibiotics—The apparent rate of degradation of penicillin G in the micellar form existing at a concentration of 500,000 units/ml was compared to that of nonmicellar penicillin G at 8000 units/ml in the 5.0–9.5 pH range (1185). In the micellar solutions, the rate of hydrogen-catalyzed degradation was increased twofold but that of water- and hydroxyl-ion-catalyzed hydrolysis was decreased two- to threefold. Consequently, the pH–rate profile of the micellar solutions was shifted to higher pH values, and the pH of minimum degradation was 7.0 compared to 6.5 for the nonmicellar solutions at the same ionic strength. Compared at their respective pH–rate profile minima, micellar penicillin G was 2.5 times as stable as the nonmicellar solution.

The partition mechanism of tetracycline in an octanol–water system was studied by measuring the change in spectral properties of tetracycline in organic solvents (1186). Only the neutral form partitioned into the organic phase, and the amount transferred out of the aqueous solution was considered to be related to the concentration of the neutral species present. The relationship between partition coefficient and microscopic ionization constants of tetracycline was also clarified. Some carboxyl-containing ethylene copolymers were prepared and exhibited long-term antibacterial and antifungal properties (1187). These compounds contained antimicrobial agents bound to the copolymer backbone as carboxylate salts and were tested for self-sanitizing properties. Tests demonstrated that these materials, although not bactericidal, inhibited microbial growth.

The crystalline properties of epicillin and ampicillin and their hydrates were compared (1188). Amphotericin B was dissolved according to the manufacturer's directions to form colloidal solutions, which were filtered through membranes of different porosity (1189). Numerous particulates were observed in the unfiltered reconstituted commercial solution. Kinetic studies were carried out on the hydrolysis and photochemical degradation of the cytotoxic agent coralyne (1190). The photochemical reaction was reduced by protecting the drug from visible light or by increasing the concentration in solution, and it was reversed by lyophilization, heating, or increasing solution pH to above 12. Other factors affecting the degradation were explored, and the mechanisms involved were discussed. A salt formed from propionyl erythromycin and sulfamethoxypy-

ridazine showed more rapid dissolution and greater bioavailability than an admixture of the two components (1191). The use of the salt in pharmaceutical preparations was recommended.

Radiopharmaceuticals—Bleomycin was radiolabeled by iodine monochloride, chloramine-T, and lactoperoxidase methods (1192). The iodine monochloride technique was preferred and produced 80% radionuclide. Hydrolytic deiodination occurred at a rate of only 1.2%/day. Inulin modified by *o*-hydroxybenzaldehyde (salicylaldehyde) and *o*-hydroxybenzoic (salicylic) acid demonstrated increased ability to bind iodine-131 and demonstrated high hydrolytic stability (1193). Gel filtration demonstrated no differences between inulin and the labeled material. The quality control of radiopharmaceuticals was discussed, and the possibilities of new tests using isotopic materials for determination of sterility and endotoxin detection were presented (1194). Reviews were published concerning the quality control of radiopharmaceuticals (1195), the status and future of radiopharmaceuticals (1196 and 1197), the production of radioisotopes for medical use (1198), the detection of radioisotopes in living bodies (1199), and the biological properties of radiopharmaceuticals (1200 and 1201).

BIOPHARMACEUTICS

Publications on biopharmaceutics are subdivided according to areas of special interest. However, in view of the overlap in subject matter, anyone interested in this subject should consider a thorough reading of the entire section.

Bioavailability of Drug Substances—Complete uptake of radioactivity from the upper part of the GI tract occurred after oral administration of tritiated digitoxin (1202). A small fraction of the absorbed material was shown to represent hydrolysis products of the drug. In another study, only two-thirds of orally administered tritiated methyldigoxin (medigoxin) was absorbed from the upper GI tract (1203). Saliva was reported to offer a convenient means for monitoring the digoxin levels in blood serum (1204). The mean saliva–serum concentration ratio in 34 patients was 1.14.

The bioavailability of alprenolol was demonstrated to be dose dependent, apparently due to a limited capacity for biotransformation before entering the general circulation (1205). The half-life after a single dose was the same as that following four doses given in a single day. Labeled butylscopolamine was measured in bile and urine following oral administration (1206). Negligible absorption was found, leading to the hypothesis that the drug acts by a local effect in the GI tract. In contradiction, a review presented information that butylscopolamine was absorbed to a considerable degree (1207). The bioavailability of nortriptyline was predicted from the use of an equation estimating first-pass metabolism from the dose, hepatic blood flow, and total area under the plasma level–time curve (1208). The predicted values for bioavailability ranged from 45 to 75%, consistent with experimentally derived estimates.

Excellent agreement was obtained between the 24- and 96-hr urinary excretion data for griseofulvin products after oral administration of a single 500-mg dose (1209). It was proposed that 24-hr cumulative total 6-desmethylgriseofulvin excretion data be used an an index of griseofulvin bioavailability in humans.

A series of monographs was published describing the bioavailability of ampicillin (1210), nitrofurantoin (1211), phenytoin (1212), prednisone (1213), tetracycline (1214), oxytetracycline (1215), digoxin (1216), and indomethacin (1217).

Methodology—Two equations were developed for employing urinary excretion data to estimate drug bioavailability (1218). The equations were examined using simulated data for both one- and two-compartment open models and were tested with literature data with excellent results. A procedure to permit bioavailability estimations at quasi- and nonsteady states was proposed (1219). Necessary requirements for its application are that drug disposition obeys linear kinetics and that succeeding doses are administered during the log-linear phase, free from the influence of continuing absorption. A demonstration was provided that the use of a two-term Taylor expansion to simplify calculations of drug absorption rates in multicompartmental systems may lead to serious errors which can be avoided if the Taylor expansion is not employed (1220).

Methodology for calculating fast and slow release drug components in sustained-release dosage forms was described (1221 and 1222). If the pharmacokinetics of the sustained dosage form and the immediate release preparation are known, two equations, one describing the duration and the other the height of the plasma concentration–time curve, were proposed. Assessment of the *in vivo* quality of a sustained-release product during the initial stages of development through the application of this procedure was proposed. Administration of immediately released drug in divided doses over time along with the comparison of matching blood level curves obtained with a sustained-release formulation was presented as a method to demonstrate the achievement of controlled drug release (1223).

The use of incomplete block designs in determining comparative bioavailability was suggested where administration of all formulations to each subject would be impractical (1224). Statistical evaluation of data so obtained was illustrated by an actual trial comparing four formulations of lithium carbonate. Equations were developed to permit the estimation of biological availability after oral drug administration for drugs eliminated by urinary excretion and hepatic metabolism (1225), and the first-pass effect through the liver was estimated by this procedure.

Three *in situ* animal models were studied to determine the effect of intestinal pH upon bioavailability (1226). Data from the rat and dog correlated well with results in humans, but results from the rabbit did not. It was suggested that the rabbit would be a poor candidate for attempted animal–human bioavailability correlations. A dialysis apparatus was designed to measure the *in vitro* availability of drug from oral liquid preparations (1227). This methodology was employed to compare availability of phenethicillin from three commercially available oral pediatric preparations. An improved column-type dissolution apparatus was de-

scribed (1228). Procedures were incorporated to eliminate blockage of the filtration system by insoluble fragments. Results with uncoated and coated tablets were analyzed to discuss problems with column-type dissolution systems.

A correlation was shown to exist between saliva and plasma levels for quinidine (1229) and amobarbital (1230). Possible effects of pH and protein binding upon results were discussed.

A review discussing methodology and factors affecting percutaneous absorption was presented (1231). The validity of using *in vitro* human skin preparations to predict *in vivo* absorption was demonstrated with 12 organic compounds (1232). Although quantitative agreement was less than perfect, a rank-order correlation was achieved. An *in vivo* method for monitoring the rate of water desorption from human forearms using dry nitrogen gas passed over the skin was investigated (1233). Experimental results confirmed an earlier finding that polysorbate 85 increased epidermal permeability.

Methodology was developed for assessing the contribution of tear turnover, instilled solution drainage, and nonproductive absorption to the loss of drug from the precorneal area of the eye (1234). Experimental data obtained upon corneal application of pilocarpine nitrate in rabbits were used to develop these projections.

A linear correlation was found between the logarithm of the *in situ* gastric absorption rate constant of 14 barbiturates with the R_m values obtained in selected reverse-phase partition chromatographic systems (1235). Possible relationships between chromatographic parameters and absorption rate constants from sites other than the stomach were explored. On the basis of pharmacokinetic simulations and experimental data, it was shown that urinary excretion measurements should be made during the 1st hr to permit adequate evaluation of absorption of aspirin from different dosage products (1236). Measurements made after 3 hr were inadequate. Results from percutaneous absorption studies conducted with hydrocortisone, testosterone, and benzoic acid correlated with results obtained in monkeys and humans (1237). Therefore, the Rhesus monkey was suggested as a suitable animal model for percutaneous absorption studies of relevance to humans.

Physicochemical Factors—A study was made of factors affecting the bioavailability of tetracycline compounds (1238, 1239). Two polymorphs each of tetracycline, chlortetracycline, and oxytetracycline were demonstrated, and their solubilities were determined. The crystal form significantly influenced the bioavailability only of tetracycline as determined by a urinary excretion study in human subjects. Administration of the free base forms produced higher plasma levels as well as greater total cumulative absorption than were obtained with the hydrochloride salts.

Blood levels after injection of an ampicillin trihydrate aqueous suspension were compared with those produced by injection of an ampicillin sodium solution (1240). The suspension produced a longer duration of activity, although higher peak levels were obtained with the solution. The phthalidyl ester of ampicillin provided serum levels in humans 2.5 times as great as those produced by ampicillin (1241). Orally administered carbenicillin indanyl sodium was readily absorbed to produce a maximum serum level within 2 hr. Higher blood levels were achieved than with carbenicillin (1242). Tissue esterases were shown to convert the ester rapidly to carbenicillin, and *in vivo* activity was attributable to the latter compound. Oral administration of pivampicillin hydrochloride to normal human subjects resulted in higher peak levels and greater total availability than were obtained with ampicillin (1243, 1244). Similar results were obtained when suspensions of the free base forms were compared. In studies comparing the bioavailability of different ester forms of ampicillin, absorption rates correlated with the lipid solubility of the ester (1245).

Both particle size and vehicle viscosity affected the bioavailability of pentobarbital (1246). Particle size was also shown to influence significantly the absorption of digoxin (1247, 1248). The bioavailability of tablets prepared with drug of 7–13-μm particle size was 78–97% of that of the drug administered in solution. Tablets prepared from 102-μm material provided only 39% of the bioavailability of the reference solution.

The use of the prodrug approach to facilitate absorption was explored in several studies, and its application to antibiotics (1249) and cytotoxic agents (1250–1252) was discussed.

The activity of local anesthetics (as hydrochlorides) in producing overturn in goldfish, measured in pH 8.0 buffer solution, was shown to increase in the following order: procaine < lidocaine < tetracaine < dibucaine (1253). The results were explained on the basis of the drug partition coefficient and the minimum effective concentration in goldfish, with only the unionized fraction of drug being responsible for the observed effects. A two-compartment open model was used to describe the buccal absorption of steroids (1254). Rate constants were calculated using a feathering technique, and an analog computer was employed to project absorption values which agreed favorably with experimental data. On the basis of a crossover experimental design, the absorption profile of griseofulvin was assessed in humans following oral administration of a 500-mg dose in capsules of the anhydrous and monochloroform solvate forms (1255). Bioavailability was significantly higher with the solvated drug, and the results correlated well with solubility and dissolution rate studies in simulated intestinal fluid.

Several reviews discussed the effects of physical and chemical properties of the drug on bioavailability (1256–1265).

Formulation Factors—Bioavailability of digoxin from different commercial and experimental products continued to be of interest during the year. Bioavailability from four randomly selected lots of digoxin produced by a single manufacturer showed no greater variability than that obtained when one lot was administered twice (1266). Intersubject variation in areas under the serum concentration–time curve and in the 24-hr urinary measurements was more than twice that of intrasubject variations. Although four brands of digoxin tablets did not differ in total absorption or total

urinary excretion in humans and were equivalent for maintenance treatment, marked differences occurred in area and steepness of the absorption curves (1267). One brand was absorbed so slowly as to be unsuitable for rapid oral digitalization.

The bioavailability of digoxin from tablets compared to *in vitro* dissolution rates showed that tablets releasing a minimum of 90% of drug within 2 hr were likely to be bioequivalent (1268). In another study, digoxin tablets having different dissolution rates were administered at 0.5 mg/day for 9 days (1269). Products that showed differences after a single dose also produced significant variations in steady-state levels. Use of a 24-hr urinary excretion was proposed as the most reliable screening test to assess bioavailability.

Rapidly dissolving digoxin tablets were shown to provide complete absorption (1270, 1271). No significant differences in urinary excretion levels were shown when the rapidly dissolving tablets were compared to a digoxin elixir. A solution of digoxin in capsule form was demonstrated to provide greater bioavailability than rapidly dissolving tablets (1272), but no explanation was offered for the results. In a bioavailability study comparing digoxin tablets produced by two major manufacturers, cumulative urinary excretion data were recommended for assessing bioavailability rather than plasma data obtained after 2 hr (1273). Storage of tablets for 2 years did not affect bioavailability. No differences were seen in the bioavailability of digoxin administered as a rapidly dissolving tablet, capsule, or oral solution in water (1274). However, administration of a pediatric elixir provided consistently higher urinary excretion levels. In comparison with an intravenous injection, only 63% of the drug was absorbed from tablets and 75% from the elixir. Finally, experimental digoxin tablets, having a wide range of dissolution rates, were shown to produce gross variations in bioavailability as determined from peak plasma concentrations, areas under the 5-hr plasma concentration–time curve, and 10-day urinary excretion results following administration of single doses (1275). Determination of dissolution rate was the best method for predicting bioavailability, and the establishment of a minimal acceptance level was proposed.

Several studies were published in which bioavailability of commercial tetracycline products was assessed. In a Canadian study, significant differences were seen in commercial products (1276). The use of 6–8-hr blood or urine data was proposed to assess bioavailability. Statistical correlations were shown between T_{60} dissolution data and blood and urine results. Bioavailability differences in other commercial tetracycline products also were reported (1277, 1278). No significant differences in the bioavailability of different brands of doxycycline capsule products were found when compared to a suspension.

More rapid and complete absorption of phenethicillin occurred from the oral aqueous solution of the potassium salt than from an oil suspension of the same material (1279). Slow and incomplete absorption occurred after administration of a suspension of the benzathine salt. Significant differences in absorption rate, peak blood level, and blood level 4 hr after administration were demonstrated in a crossover study of 11 brands of phenoxymethyl penicillin (penicillin V) (1280).

Urinary excretion of acetaminophen after rectal administration of three suppository formulations was compared to that after oral administration of a tablet dosage form (1281). Rectal absorption showed extreme variability, and relative bioavailabilities of from 68 to 88% were obtained compared to the oral tablet. Differences in absorption rates from the suppository products were great, and in one case the clinical efficacy of the product would be questioned.

No significant differences were found in the bioavailability of three dexamethasone tablet products, and the results were essentially identical to those from an elixir formulation (1282). Statistical differences were shown in the rate of appearance of prednisolone in plasma but not in the total amount converted to prednisolone following administration of three commercial prednisone tablets to volunteers (1283, 1284). The results suggested that differences in *in vivo* rates of appearance of prednisone be employed to assess bioavailability and be compared to *in vitro* dissolution rates.

The influence of crystal size (macro or micro) and dosage form (capsule or tablet) on urinary excretion of nitrofurantoin was investigated in 20 subjects (1285). Higher urinary excretion levels were obtained from tablets. Differences in crystal size affected urinary excretion when the drug was administered in capsules. Side effects appeared equally with all preparations.

Blood levels determined following oral administration of single doses of three commercially available brands of chlorpropamide revealed significant differences between products (1286). Two tolbutamide products also differed markedly in the serum concentration–time curves produced following oral dosing (1287). Differences in serum levels were obtained with sulfadiazine tablets from different manufacturers, although *in vitro* release values of the products were comparable. The relationship between the bioavailability of fluorides and their anticaries effectiveness was discussed (1288). A comparison was made between two groups of studies, one in which sodium fluoride was reported to be effective and another in which it was reported to be ineffective.

The percutaneous absorption of hexachlorophene following daily whole body washings was employed to compare the bioavailability of two commercially available detergent-based skin-cleansing products (1289). Differences were demonstrated between the products, and blood level data demonstrated considerable absorption. There was no correlation between whole blood concentration, body surface area, or skin pigmentation.

The period following administration over which blood level measurements should be made to obtain a reliable bioavailability comparison of two or more formulations of the same drug was examined on the basis of literature data for a number of drugs (1290). For most drugs, ratios of areas under the curve changed little between the end of the absorption period and the time when blood sampling was terminated. It was suggested that reliable bioavailability comparisons among different brands

could be made by blood sampling over 24 hr or less.

The percutaneous absorption of anthralin and its triacetate was investigated through the use of tritium-labeled drugs (1291). Four ointment vehicles were evaluated, and depth of penetration was determined by stripping skin layers with cellophane tape. The best penetration occurred through hydrophobic ointments. Absorption of anthralin was superior to that of the triacetate compound. The depth of penetration of coal tar and ichthammol into rabbit skin also was determined by the stripping method (1292). The deepest penetration of the tar occurred from a water-in-oil low fat base, while the best absorption of ichthammol was from petrolatum.

In another study of percutaneous absorption, the penetration of salicylic acid with and without dimethyl sulfoxide decreased as the ointment vehicle pH was increased (1293). The topical absorption and retention of salicylic acid and carbinoxamine from four oil vehicles followed first-order kinetics after an initial lag phase (1294). The vehicle with the strongest affinity for the drug demonstrated the poorest absorption. Higher absorption rate constants were observed through excised skin than intact skin. Measurement of total radioactivity in the blood of rats for 5 hr following rectal administration of tritiated benzocaine in ointment vehicles demonstrated that the greatest release occurred from the water-soluble vehicle (1295).

The bioavailability of vitamin E administered intramuscularly was determined by comparing free tocopherol levels in blood after administration of aqueous micellar dispersions of tocopherol and tocopherol acetate (1296). The rate-limiting step in the bioavailability was shown to be the rate of hydrolysis of the acetate ester to the physiologically active free tocopherol, and vitamin E activity in blood was much greater when the free alcohol was administered. The use of lipids such as cholesterol, cholesteryl acetate, and β-sitosterol as carriers for oral and implantation therapy was investigated (1297). *In vitro* and *in vivo* studies demonstrated the usefulness of this approach. Naltrexone–poly(lactic acid) composites demonstrated effective blocking action to morphine in animals for 20–29 days (1298).

Effects of surfactants on the intramuscular absorption of a water-soluble drug were investigated (1299). Inhibitory effects were shown to occur in the presence of both ionic and nonionic surface-active agents. A morphine implantation pellet prepared by adsorbing morphine sulfate onto a molecular sieve induced physical dependence in mice (1300). The pellet was implanted subcutaneously, and the peak of physical dependence occurred within 24 hr after implantation.

An attempt was made to employ liposomes for prolonging intramuscular absorption of highly water-soluble drugs (1301). After injection in the form of liposomal suspensions, clearance of model drugs from the injection site was considerably delayed in comparison with the controlled aqueous buffer injections. The larger the amount of cholesterol incorporated into the liposomes, the slower the drug absorption became. Hydrolysis of liposomes at the injection site appeared to be responsible for the greater *in vivo* release than was predicted from *in vitro* results.

The influences of concentration and vehicle composition on corneal penetration of the steroid fluorometholone were studied in the albino rabbit (1302). A sustaining effect noted upon instillation of a micronized drug suspension was attributed to the retention of particles within the cul-de-sac of the eye. When an ointment preparation was employed, the peak aqueous humor concentration was not achieved until 3 hr after administration. Predosing with a saturated solution followed by application of the ointment was recommended to achieve an immediately effective concentration followed by a sustaining effect.

The influence of drainage and tear turnover was studied through the administration of radioactive technetium Tc 99m sulfur colloid in the presence of topical anesthetics (1303). Reduction in the tear turnover rate varied for different anesthetics and was dose dependent. Aqueous humor concentration–time profiles for radioactive pilocarpine nitrate in the presence and absence of topical anesthesia verified the importance of tear turnover and instilled solution drainage as the major routes of drug loss in the eye. The effect of methylcellulose and polyvinyl alcohol as viscosity enhancers in ophthalmic preparations was explored, and a viscosity range of 12–15 cps was reported as optimum for prolonging contact time (1304). A study of the ophthalmic efficacy of dexamethasone showed that a suspension of the alcohol was more effective in suppressing inflammation than an equal quantity of the phosphate solution, whereas the solution was more effective than the phosphate ointment (1305).

Soft contact lenses saturated with tritiated pilocarpine provided greater activity in the aqueous humor for up to 6 hr compared to a topically applied pilocarpine solution (1306). The application of drug bioavailability input and pharmacological response output results in designing drug delivery systems was discussed (1307), and this approach was exemplified with two antiglaucoma drugs.

Micronized griseofulvin administered in a corn oil-in-water emulsion demonstrated significantly enhanced bioavailability compared to an aqueous suspension and a commercial tablet dosage form (1308, 1309). A mechanism based on the ability of linoleic and oleic acids liberated during the digestion of corn oil to inhibit GI motility and stimulate gallbladder evacuation was proposed. Although the onset of absorption after administration of the corn oil emulsion was delayed, this difference in comparison with the aqueous suspension disappeared after multiple dosing of the two dosage forms.

Enhanced bioavailabilities of sulfisoxazole acetyl and dicumarol were found when the drugs were administered in lipids as compared to administration in water (1310). The absolute bioavailability of griseofulvin was increased by coadministration with polysorbate 80 in which the drug was quite soluble. An attempt was made to correlate polarity, micelle-forming properties, digestibility, and chylomicron-forming properties of lipid vehicles with their effect on drug bioavailability. Emulsifier effects upon the absorption of vitamin A acetate and phenylbutazone were studied (1311). Absorption of vitamin A acetate was found to occur *via* the

micellar phase, whereas the free concentration in the aqueous phase was the determining factor for phenylbutazone. The effect of surfactants, tetracycline, and edetic acid (EDTA) upon intestinal mucosal integrity was studied by intravenously administering sulfaguanidine to rats and monitoring the concentration of drug appearing in the intestinal lumen (1312). Except for poloxamer 188[15], all agents studied had a damaging effect upon the intestinal walls.

Administration of dioctyl sodium sulfosuccinate markedly enhanced the GI absorption of phenolsulfonphthalein in rats (1313). This result appeared to be due to altered permeability of the intestinal mucosa. In contrast, poloxamer 188 showed no potentiating activity. At higher concentrations, both surfactants decreased absorption, presumably due to micellar drug entrapment. Several nonionic and anionic surfactants increased thioridazine absorption in goldfish (1314). This effect occurred at or near the CMC. Above this level, the surfactants had a decreasing effect on absorption.

A study of the effect of alcohol upon theophylline absorption showed that, in contrast to results obtained in rats, ethanol produced no enhancing effect upon average plasma levels of theophylline in humans (1315, 1316). Other alcohols, namely methanol, 1-butanol, glycerin, propylene glycol, and, to a lesser extent, mannitol and sorbitol, increased net water flux from the small intestine of rats, thereby increasing the rate of theophylline absorption. Evaluation of the effects of normal alcohols on intestinal absorption of salicylic acid, sulfapyridine, and prednisolone in rats showed that the presence of alcohol produced dissimilar absorption rates for the drugs studied (1317). In view of the results, the absorption-altering effects of the alcohol could not be attributed solely to increased water flux. Although a 25–50-fold molar excess of trichloroacetate increased the disappearance of methantheline bromide from intestinal loops, the onset of mydriasis in animals appeared to be delayed in the presence of trichloroacetate (1318). Administration with sodium lauryl sulfate and methylcellulose increased the absorption of aspirin, salicylic acid, and sulfadimidine (sulfamethazine) in rats (1319). Absorption was greater from oral solutions than from suspensions.

Although a qualitative correlation was found between the *in vitro* dissolution rate and the calculated initial absorption rate constants for prednisone, *in vitro* dissolution rates were not predictive of the overall bioavailability of the tablets tested (1320). A sustained-release capsule containing 20 mg of isosorbide dinitrate produced blood levels similar to 5 mg of an immediate release dosage form administered four times at 3-hr intervals (1321). Peak nitrate serum levels were reached in the 9th hr. Administration of a slow release procainamide tablet every 8 hr produced about the same mean plasma level at steady state as ordinary tablets given every 4 hr (1322, 1323). Occasional high plasma concentration peaks observed after administration of nonsustained-release tablets did not occur when the slow release product was administered. When a 180-mg sustained-release pseudoephedrine hydrochloride tablet was administered twice daily, plateau plasma levels were reached after 3 days (1324). An initial increase in heart rate and insomnia disappeared within 3 days.

A prolonged-acting quinidine bisulfate tablet provided more stable serum levels and less GI reactions than immediate release tablet products (1325). A crossover study was conducted to compare the bioavailability of amitriptyline administered as a 25-mg tablet three times daily with a 75-mg sustained-release pelletized form (1326). Blood levels were essentially equivalent after 1 week. No difference was demonstrated between the absorption of ferrous sulfate from an immediate release tablet and a slow release form in normal subjects and anemic patients (1327). Ascorbic acid enhanced iron absorption, especially in anemic postgastrectomy patients. The duration of the neutralizing effect in human subjects of a slow release antacid tablet was demonstrated to be 300% greater than that of the simple antacid (1328). In the slow release product, calcium carbonate was incorporated into wax-containing granules.

Differing Administration Routes—In volunteers administered imipramine orally and parenterally, higher levels of the metabolite desipramine occurred after oral dosing (1329). The therapeutic consequence of this difference was discussed. Although intravenous propantheline lowered blood ethanol levels after ingestion of a standard ethanol load, oral doses were without significant effect (1330). The marked reduction in oral bioavailability should be considered in clinical situations. Absorption of naproxen from water-soluble and fat-based suppositories were comparable to absorption from an equivalent oral dose (1331). Indomethacin was well absorbed after oral dosing, and peak plasma concentrations were achieved within 2 hr (1332). Comparison with the area under the curve after intravenous dosing indicated that complete bioavailability was achieved by the oral route. Although complete absorption occurred following rectal administration, the rate was slower than after oral dosing.

Comparison of plasma phenytoin concentrations in an intravenous and intramuscular crossover study showed that the intramuscularly administered drug was absorbed over 5 days (1333). A model simulating precipitation and redissolution of the drug at the injection site provided a satisfactory fit for the observed plasma concentrations. Rectally administered proxyphylline was shown to fit a two-compartment open model, whereas oral administration conformed to a one-compartment model system (1334). The drug appeared to be well absorbed by both routes. The blood concentration of chlordiazepoxide hydrochloride was higher after oral administration of a 50-mg dose than after intramuscular injection of 100 mg (1335). Peak levels of the metabolite were similarly lower after injection. Oral and intramuscular administrations of nortriptyline hydrochloride provided equivalent blood levels (1336). These results demonstrated complete GI absorption.

Subcutaneous disappearance of lidocaine hydrochloride was followed as a function of time using a closed absorption cell affixed to anesthetized rats (1337). A shift of the solution to higher pH values within the cell suggested that precipitation of lidocaine base occurred in some experiments.

No measurable radioactivity was found in serum after dermal application of clotrimazole as a 1% cream or solution (1338). Less than 0.5 and 0.05% of the radioactivity applied to the skin in the cream and solution, respectively, were excreted in the urine within 4–5 days. Following vaginal application of the solution, serum concentrations of only 0.2% of those obtained after oral administration were observed. Factors influencing the bioavailability of drug products administered by different routes of administration were reviewed (1339).

Physiological Factors—Significant intersubject variability was observed in the cumulative excretion in urine after 7 days and in the area under the 24-hr serum concentration curve following single-dose administration of 0.5 mg of digoxin (1340). A significant correlation existed between cumulative digoxin excreted during the first 2 days compared to 7-day excretion data. Use of cumulative 2-day excretion data following single-dose administration was recommended to compare bioavailabilities of oral digoxin preparations. A review was published in which a magnesium trisilicate antacid product was found not to affect digoxin bioavailability in dogs (1341). These results contradicted previous findings in which the dissolution of digoxin was completely suppressed by the antacid. In contradiction to a previous study, one report indicated that phenylbutazone absorption was not adversely affected by antacids (1342).

Enhancement of *in situ* absorption of several drugs from the rat small intestine occurred upon perfusion of drug with hypotonic solutions, whereas hypertonic solutions diminished drug transfer (1343). The rate of intestinal blood flow also played an important role in the absorption of drugs that were lipid soluble and very rapidly absorbed. Ephedrine hydrochloride administered orally to mice was more rapidly absorbed from isotonic glucose than from isotonic sodium chloride (1344, 1345). This result was attributed to the effect of glucose in facilitating transmucosal fluid uptake. Reduction in mesenteric blood flow rates resulted in impairment of sulfaethidole absorption in an *in situ* canine intestinal preparation (1346). Haloperidol absorption also decreased with decreased intestinal perfusion but differed from sulfaethidole in that membrane storage of haloperidol appeared to take place during its absorption.

Absorption rates of salicylate and antipyrine across the rat gut intestine were reduced under the influence of fasting (1347). Mucosal cell viability, cell number, and mesenteric blood flow were considered to be major factors affecting drug absorption rates. In another study, the diminished volume of distribution induced by fasting was considered to be a major cause of the decrease of drug absorption from the intestines of fasted rats (1348). Reduced absorption rates in fasted rats were also demonstrated with salicylic acid and antipyrine (1349). In this study, the effect was attributed to inhibition of intestinal cell proliferation during fasting, resulting in a decreased absorptive surface.

Absorption of theophylline was more rapid when administered following a high protein meal than after a high fat or high carbohydrate meal (1350). Absorption from solution was faster than from a solid dosage form in all treatments studied. An increase in the bioavailability of nitrofurantoin coadministered with propantheline was attributed to a delay in gastric emptying (1351). Administration of atropine sulfate significantly increased the time necessary to achieve peak blood levels of lidocaine (1352). This delay was also attributed to a gastric emptying inhibition effect. Increased absorption of indomethacin occurred with coadministration of buffered aspirin in healthy volunteers (1353). Concomitant administration of aminosalicylic acid delayed peak blood serum levels of rifampicin (rifampin) and decreased by half the area under the absorption curve (1354). The conclusion was reached that this combination of drugs is not suitable for routine tuberculosis therapy.

Marked intersubject variability was found in the ratio of saliva to serum concentration of procainamide in 12 chronically medicated patients (1355). There was no correlation between the dose administered and the minimum serum or saliva concentration. The ratio of saliva to serum concentration increased with decreasing saliva pH. This result was largely explained by the pH-dependent ionization and distribution of the drug. Evaluation of serum concentrations and urinary excretion data indicated the occurrence of a sex difference in the rate and extent of cephradine absorption from three injection sites (1356). Smaller areas under the curve occurred in female patients. The proportion of a dose of meperidine excreted unchanged or as metabolite was found to depend upon the urinary pH and the route of administration (1357). Older people appeared to metabolize more of the drug and excrete less in unchanged form. Excretion of the drug in acid urine was directly proportional to the plasma concentration.

A widely used carbonated beverage and an antiemetic product containing carbohydrates and phosphoric acid, when administered together with riboflavin 5-phosphate or salicylamide, significantly increased the bioavailability of riboflavin and appreciably altered the metabolic fate of salicylamide by increased conversion to the sulfate and decreased formation of the glucuronide (1358). These effects were attributed to the decreased gastric emptying rate caused by the carbohydrates and phosphoric acid, consistent with the empirical use of these products as antinauseants and antiemetics. The results demonstrated that the choice of beverage taken with medication can affect the bioavailability and/or metabolic fate of the drug. In the presence of mucin, an approximately 50% reduction in the bioavailability of tetracycline was found in everted rat gut and diffusion cell studies (1359, 1360). The results suggested that the drug is bound to the mucin macromolecule.

Pretreatment of healthy subjects with metoclopramide, a stimulator of gastric and intestinal motility, increased L-dopa (levodopa) absorption (1361). This increase was attributed to rapid stomach emptying, facilitating absorption in the small intestine where an active transport mechanism takes place. A study of the variability of L-dopa absorption in healthy fasting subjects showed that peak plasma levels ranged from 0.25 to 2.42 mg/ml and occurred 0.5–4 hr after ingestion (1362).

Table XXX—Additional References on Bioavailability

Reference	Topic
1367	Bioavailability as an international problem with reference to digoxin
1368	Bioavailability and elimination of β-methyldigoxin (medigoxin)
1369	Absorption and biotransformation of topically applied adenosine monophosphate
1370	Bioavailability in humans of ICRF-159, an antineoplastic agent
1371	Bioavailability in humans of *N*-acetylprocainamide
1372	Review of corticosteroid bioavailability
1373	Review of *in vivo* laboratory techniques to assess bioavailability
1374	*In vitro* bioavailability testing
1375	Review of methods for bioavailability testing
1376	*In vitro* tests for determination of antacid activity
1377	*In vitro* antacid and antipepsin activity of hydrotalcite
1378	GI absorption of anticholinergic drugs
1379	Preparation, hydrolysis, and oral absorption of *d*-carboxy esters of carbenicillin
1380	Comparative release rates of depot fluphenazine injections
1381	Effect of probenecid on serum half-life of cefoxitin and cephalothin
1382	Biological availability and alteration of silybin (silymarin)
1383	Bioavailability of lysine salt of cephalexin after intramuscular injection
1384	Chemical significance of differing absorption rates of diazepam and oxazepam
1385	Bioavailability of digoxin preparations
1386	Comparative bioavailability of sustained-release quinidine preparations and quinidine bisulfate
1387	Comparative *in vitro* dissolution of quinidine tablets
1388	Comparative bioavailability of penicillin V pediatric products
1389	*In vivo* comparison of bioavailability of two ampicillin trihydrate products
1390	Bioavailability of two oral erythromycin stearate formulations
1391	Biopharmaceutical assessment of phenylbutazone and indomethacin preparations
1392	*In vitro* and *in vivo* evaluations of phenylbutazone tablets
1393	Comparative effectiveness of two brands of phenothiazine
1394	Comparative bioavailability of two oral diazepam products
1395	Comparative human bioavailability of three rifampicin (rifampin) products
1396	Evaluation of bioavailability of 13 hydrochlorothiazide products
1397	*In vivo* comparison of two lidocaine preparations
1398	Discussion of bioavailability comparisons between different manufacturers and different lots of product
1399	Bioavailability of meperidine using urinary excretion
1400	Urinary excretion studies of coated sulfamethazine
1401	Enhancement of skin absorption by poly[2-(methylsulfinyl)ethyl acrylate]
1402	Biopharmaceutical studies on nitrofurantoin
1403	Biopharmaceutical evaluation of calcium gluconate
1404	Dissolution and absorption of aspirin tablets
1405	Comparative absorption and pharmacokinetics of immediate and slow release proxyphylline tablets
1406	Effect of solution viscosity on ophthalmic activity of cocaine and pilocarpine
1407	Effect of formulation on ophthalmic activity of neomycin
1408	Formulation effects upon oral activity of indoprofen (K4277), a new nonsteroid anti-inflammatory agent
1409	Effect of microencapsulation of aspirin upon bioavailability and gastric irritation
1410	Correlation of aspirin dissolution from enteric-coated tablets on *in vivo* absorption
1411	Influence of base upon bioavailability of acetaminophen from suppositories
1412	Comparison of bioavailability of lithium carbonate and a slow release lithium sulfate preparation
1413	Influence of changes in formulation and urinary pH upon bioavailability and excretion of diethylpropion
1414	Comparative bioavailability of oral immediate and slow release iron preparations
1415	Bioavailability of fluoride
1416	Bioavailability of timed-release orciprenaline (metaproterenol) sulfate
1417	Bioavailability of isoniazid in a liquid dosage form
1418	Rectal absorption of a coated aspirin suppository
1419	Effect of formulation on absorption of naproxen suppositories
1420	Effect of lactose on increasing dissolution rate and absorption of a narcotic analgesic (Ro-03-4661) from capsules
1421	Mechanism of intestinal absorption of drugs from emulsions
1422	Enhanced intestinal absorption of methyl orange administered in emulsions
1423	Role of bile in lymphatic transport of lipid-soluble drugs
1424	Comparative bioavailability of cyanocobalamin from capsules and tablets
1425	Slow absorption of phenytoin after intramuscular injection
1426	Comparative bioavailability from tablets and capsules
1427	Effect of implantation on physical properties of silicone rubber
1428	Effect of muscle blood flow upon drug absorption
1429	Review of bioavailability of drugs administered in enteric-coated gelatin capsules
1430	Review of pharmacokinetic aspects of controlled drug delivery systems
1431	Review of rectal absorption of drugs from suppositories
1432	Effect of formulation on dissolution of aminosalicylic acid tablets
1433	Review of the role of biopharmaceutical studies in drug optimization
1434	Effect of suppository bases on antibiotic bioavailability
1435	Influence of vehicle on penetration of steroids through skin
1436	Effect of emulsions in enhancing transport of mitomycin C administered parenterally
1437	Serum levels of ampicillin and dicloxacillin after injection by intravenous and intramuscular routes
1438	Effects of different routes of administration of microencapsulated enzymes
1439	Pharmacokinetics of ascorbic acid administered rectally and intravenously
1440	Review of GI drug absorption
1441	Review of effect of food on drug absorption
1442	Effect of phenformin on calcium absorption
1443	Inhibition of rifampicin (rifampin) absorption by bentonite
1444	Effect of epinephrine in lowering blood concentrations and prolonging anesthesia of lidocaine administered by pudendal block
1445	Factors affecting absorption of drugs across rat intestines

(continued)

Table XXX—*(Continued)*

Reference	Topic	Reference	Topic
1446	Effect of fasting and antineoplastic agents on intestinal absorption of drugs in rats	1462	Review of bioavailability from pharmaceutical dosage forms
1447	Meal interference with orally administered antibiotics	1463	Comparative bioavailability of chlorpromazine oral dosage forms determined by pharmacological response data
1448	Increase in absorption of drugs in rats by exposure to light	1464	Subject variation in oral absorbability of ampicillin
1449	Increased absorption of L-dopa (levodopa) attributed to ion intestinal decarboxylation	1465	Effect of route of administration on chlordiazepoxide serum levels
1450	Biopharmaceutic influences on anticholinergic effects of propantheline	1466	Variation in bioavailability of two orally administered ampicillin trihydrate products
1451	Review of cutaneous absorption of pharmaceuticals	1467	Pharmacokinetics of five ampicillin preparations
1452	Review of pathological and physiological factors affecting bioavailability and pharmacokinetics	1468	Bioavailability of four doxycycline products
1453	Review of pharmacological modification of drug absorption processes	1469	Absorption and elimination of orally and parenterally administered tetracycline compounds
1454	Review of GI drug absorption	1470	Excretion of cephapirin after intramuscular administration
1455	Pitfalls in interpreting bioavailability data	1471	Effect of food type on absorption of zinc sulfate
1456	Review of effects of route, dosage regimen, and delivery system on drug activity	1472	Effect of cationic drugs on intestinal absorption of pralidoxime iodide
1457	Review of biopharmaceutical aspects of drug research	1473	Enhancing effect of rifampin on warfarin excretion
1458	Review of biopharmaceutics and pharmacokinetics in professional practice	1474	Pharmacokinetics of ampicillin in cirrhotic patients
1459	Review of problems in bioavailability assessment	1475	Effect of drugs and excipients on aspirin absorption
1460	Review of biological availability of drugs	1476	Review of factors affecting GI drug absorption
1461	Discussion of factors affecting bioavailability		

The importance of determining the biopharmaceutics and pharmacokinetics of new drug products to permit correlation with safety and activity was discussed (1363). Differences in individuals with respect to absorption, distribution, and elimination patterns were suggested to account for deviations from ideal dose–response relationships.

Blood concentrations of acetaminophen following oral administration of a short chain ester, *p*-acetamidophenyl acetate, were not significantly different from those found using acetaminophen (1364). Lower blood levels occurred when intermediate hydrocarbon chain-length compounds were administered. A direct relationship appeared to exist between *in vitro* hydrolysis rates and blood concentrations *in vivo*. Concomitant oral administration of acetaminophen derivatives, pancreatic lipase, and calcium salts resulted in an increase in the blood levels of acetaminophen as compared to administration of the esters alone. A combination of short chain and longer chain esters of the drug provided a prolonged release, which maintained therapeutic blood concentrations for 13 hr following a single administration in dogs.

Elevated free serum iodide levels were determined in burn patients treated topically with povidone-iodine (1365). Iodine absorption was suggested as a possible cause of unexplained abnormalities, including acidosis and renal failure, in patients so treated. Following a shower employing a whole body lather with soap containing 2% triclocarban, about 0.23% of the drug was recovered in the feces over 6 days and 0.15% in the urine over 2 days (1366). No detectable levels were found in the blood.

Additional references relating to bioavailability are found in Table XXX.

PHARMACOKINETICS

A general disposition equation for a linear mammillary model consisting of n compartments was derived and employed to develop models based upon drug administration into the central compartments and into a peripheral compartment (1477). Equations describing the time course of a drug in a particular compartment after administration by various routes were also presented. An empirical equation not based upon compartment modeling was developed to describe pharmacokinetic behavior (1478). The proposed method provided superior correlations to those obtained with a one-compartment model and could be employed to describe the time course behavior of a highly protein-bound drug for which a one-compartment model failed. An analog computer was employed to generate pharmacokinetic data, and the use of radiolabeled drugs and computers to obtain pharmacokinetic parameters was discussed (1479). Quinidine administration to rabbits was used to illustrate the application of analog computers to generate pharmacokinetic information (1480).

Novel hydrodynamic models for distribution of intravenously administered drugs was presented and compared to the conventional compartmental pharmacokinetic modeling systems currently employed (1481, 1482). The superiority of the new procedure was discussed. The application of the Loo–Riegelman absorption method was discussed by Wagner, who also reviewed problems encountered in attempting to develop pharmacokinetic models (1483, 1484). Lemberger, in discussing pharmacokinetic toxicity, recommended that the B/S level should be kept to a minimum (1485).

Table XXXI—Additional References on Pharmacokinetics of Digitalis Glycosides

Reference	Topic
1510	Serum and urine concentrations after oral administration of β-methyldigoxin (medigoxin)
1511	Physiological distribution of digoxin in the heart
1512	Influence of heart failure on serum digoxin levels
1513, 1514	Ratio between myocardial and plasma digoxin levels
1515	Effect of propantheline, metoclopramide, and L-dopa (levodopa) on serum digoxin levels
1516	Metabolism and body distribution of digoxin
1517	Review of digitoxin serum levels and elimination
1518	Digoxin levels in patients with atrial fibrillation
1519	Effect of cardiopulmonary bypass on plasma digoxin levels
1520	Ratio between myocardial and serum digoxin levels
1521	Digitalis pharmacokinetics and metabolism
1522	Formation and disposition of bis- and monoglycosides after 4‴-*O*-methyldigoxin (medigoxin) administration
1523	Renal excretion of digoxin
1524	Biliary excretion and enterohepatic circulation of digitoxin
1525	Review of digoxin pharmacokinetics and metabolism
1526	Review of digitoxin pharmacokinetics and metabolism
1527	Review of pharmacokinetics of ouabain and acetylstrophanthidin
1528	Review of pharmacokinetics of lanatoside C and methyldigoxin (medigoxin)
1529	Pharmacokinetics and metabolism of digitoxin
1530	Effect of intestinal blood flow on enterohepatic circulation of digitalis glycosides
1531	ECG changes and plasma digoxin levels
1532	Role of renal failure in digoxin pharmacokinetics
1533	Biliary excretion and enterohepatic circulation of digitoxin and metabolites
1534	Relationship between serum and saliva digoxin concentrations
1535	Pharmacokinetics of digoxin after intravenous bolus and infusion doses
1536	Pharmacokinetics and metabolism of digoxin in patients with hepatitis
1537	Determinants in renal clearance of digoxin
1538	Effects of antituberculosis drugs on digitoxin pharmacokinetics
1539	Plasma half-life following repeated administration of β-acetyldigoxin
1540	Plasma half-life following repeated administration of β-methyldigoxin (medigoxin)
1541	Serum concentrations of digoxin in infants following overdosing
1542	Influence of renal function on digitoxin pharmacokinetics
1543	Disposition and pharmacokinetics of digoxin after intravenous administration

A multicompartmental model was employed to predict organ and plasma concentrations of antileukemia drugs after administration to animals, and new therapeutic strategies based upon the results were suggested for therapy in humans (1486). A new method for multicompartment pharmacokinetic analysis was described in which a simple treatment of cumulation processes in the central compartment was performed to avoid full analysis of the system (1487). The method reduces complex accumulation calculations to the simplicity of single-compartment formulas. A one-compartment model designed to predict alterations in persistence of drugs in uremic patients was constructed using information obtained from normal subjects. For the drugs examined, the model was able to predict overall elimination rate constants in severe uremia with an error of 10% for 12 drugs and of 20% for seven additional drugs (1488). The model was proposed as a useful approach for predicting dosage adjustment in uremic patients for drugs for which data are not available.

Several articles reviewed the principles of pharmacokinetics and the applicability of pharmacokinetic data to drug therapy (1489–1509).

As in recent years, considerable attention was devoted to the uptake, metabolism, distribution, and excretion of digitalis glycosides. A listing of these studies is provided in Table XXXI.

Serum and urine data were employed to study the elimination of diphenylhydantoin (phenytoin) from children administered excessive doses of the drug (1544). Nonlinear regression analysis using a one-compartment pharmacokinetic model was employed. A trend toward relatively lower K_M and higher V_{max}/K_m values was seen in the patients. A computer program was developed to provide complete pharmacokinetic analysis of blood ethanol level data (1545). Lower peak blood levels and decreased areas under the concentration–time curve resulted when ethanol was administered with fats or carbohydrates (1546).

Plasma nortriptyline concentrations were assayed in four subjects after intravenous infusion (1547). Best-fitting curves were obtained using a two-compartment open model. A pharmacokinetic study of nortriptyline was performed using oral and intravenous dosing (1548). Only 46–59% of the orally administered drug was systemically available. This level was attributed to metabolism following administration. Quantitative measurements of first-pass metabolism also were obtained from urinary metabolite excretion data when the kinetics of metabolite formation and elimination were taken into account. Analysis of data from the intravenous test according to a two-compartment open model showed close correlation between the rate constant of distribution from the central to the peripheral compartment and the elimination rate constant in the central compartment.

A linear relationship was demonstrated between the elimination rate constant of sulfadiazine and the endogenous creatinine clearance in patients with normal and impaired kidney function (1549). The mean half-life of the drug was 10 hr in normal patients and 22 hr in anuric patients. The plasma phenytoin half-life following intravenous administration was 14.5 hr (1550). Following oral administration, peak plasma concentrations were reached in 4–12 hr. Steady-state plasma levels varied considerably among individuals after multiple oral doses and exceeded those predicted from a single intravenous dose by 29–77%. This discrepancy was attributed to transition to dose-dependent kinetics. The heparin half-life in blood was about 1.5 hr and did not increase with dose (1551). Differences in four methods used for measuring heparin pharmacokinetics were discussed. Treatment of healthy volunteers with allopurinol and clofibrate did not alter the plasma

warfarin elimination rate (1552). Enhancement of warfarin activity by clofibrate in humans was thus attributed to interaction at the receptor site. Treatment with allopurinol resulted in significant prolongation of the plasma dicumarol half-life.

To investigate the effect of end-stage renal insufficiency and hemodialysis on the serum procainamide half-life, 500 mg was administered orally to control subjects and dialysis patients (1553). The mean half-life in normal subjects was 3.2–3.5 hr *versus* 11.3–16 hr in the patients. Mean plasma acetaminophen and phenacetin half-lives were approximately 15% longer in normal male volunteers at 6 am than at 2 pm (1554). The apparent volume of distribution decreased by about 13% from 6 am to 12 pm, whereas the mean metabolic clearance rate did not change significantly. Although plasma half-lives at these hours were highly reproducible within a given subject, much individual variation occurred. Only a maximum of 10% orally administered acetaminophen was metabolized during the first pass through the liver (1555).

The pharmacokinetics of acetaminophen in 2–3-day-old full-term infants showed the half-life to be 3.5 hr compared with 1.9–2.2 hr observed in adults (1556). The rate constant for glucuronide formation in neonates was considerably smaller than in adults, whereas the rate for formation of sulfate was somewhat larger than in adults. The limited ability of neonates to conjugate phenolic drugs with glucuronic acid appears to be partially compensated for by a well-developed capability for sulfate conjugation.

Individual plateau serum salicylate levels correlated better with urinary excretion rates of the metabolite, salicylurate, than with total urinary excretion of salicylates (1557). This finding suggested that large intersubject variations in plateau serum salicylate levels may be attributable to differences in maximum rates of a capacity-limited metabolic reaction. For optimal therapeutic response, individualization of aspirin dosing by following serum salicylate levels was recommended. The use of 2-*p*-aminobenzoyloxybenzoic acid as a prodrug was suggested, since it is well absorbed from the GI tract and hydrolyzed to salicylic acid in blood and tissues (1558). However, 50% of the dose was excreted unchanged in urine.

The pharmacokinetics and metabolic fate of gentisic acid in humans were investigated (1559). The compound was excreted unchanged in urine with an elimination half-life of 1.4–2.6 hr. In normal male subjects, the half-lives of antipyrine, aminopyrine, and phenacetin were not significantly different from the half-lives of each drug in saliva (1560). Apparent volumes of distribution in plasma and saliva differed by the extent to which each drug is bound to serum protein. General equations were used to show the relationship between the half-life for elimination of the parent drug from the body and the rate of excretion of metabolites. The salivary half-life of antipyrine is used as a convenient procedure for estimating the relative rates of drug metabolism in humans (1561). The elimination of antipyrine from saliva was shown to be a useful index of drug metabolism in animals and humans.

A study of the biological disposition of methadone in acute and chronic administration suggested that both dispositional and pharmacological tolerance are involved in the development of tolerance following chronic administration (1562). In the acute study, a biexponential plasma methadone level decay was observed. The acute primary half-life of 14.3 hr in combination with the acute secondary half-life of 54.8 hr was longer than the single exponential product half-life of 22.2 hr determined in the same subjects. In six patients given increasing doses of methadone during a 1-month period, the ratio of the *N*-monomethylated metabolite to the parent drug increased and the urinary recovery of unchanged methadone decreased (1563). In addition to methadone, seven metabolites were isolated and identified in urine and three metabolites were found in feces.

The plasma concentration–time profiles of meperidine following intravenous injection were investigated by reference to a classical two-compartment open model (1564). When administration proceeded induction of anesthesia, induction was consistently followed by an increase in venous plasma concentration that prevented classical kinetic analysis. Increasing alcohol consumption by patients was associated with increasing volumes of distribution, and an increased fraction of drug unbound in plasma occurred with increasing patient age. The disposition of morphine following administration of 10 mg/kg was determined by a sensitive and specific radioimmunoassay in 31 anesthetized patients (1565). Following intravenous injection, 93% of the morphine disappeared from the serum within 5 min. The 2-min serum levels of the drug correlated directly with the patients' ages. The serum half-life between 10 and 240 min was independent of age and averaged about 2 hr. Following intramuscular administration, the drug was rapidly absorbed and peak levels occurred within 10–20 min. The decline in serum levels paralleled the decline in analgesia and was coincident with the appearance of morphine glucuronide in the serum.

The urinary excretion of free naltrexone and its major urinary metabolite was 1.2 and 26.3% of the administered dose, respectively (1566). The urinary excretion of conjugated drug and the metabolites was 9.7 and 16.4%, respectively. The half-life of naltrexone was determined to be 1.1 hr, whereas that of the metabolite was 14–18 hr. A multicompartment model was developed for the pharmacokinetics of adriamycin (doxorubicin) (1567). On this basis, human plasma levels were predicted and a comparison with patient data demonstrated reasonably good correlation.

A GC procedure was found to be more reliable than the UV procedure previously employed for pharmacokinetic studies of theophylline. By using this procedure, a half-life of 11 hr was determined and the pharmacokinetics were described by a two-compartment model (1568). Considerable individual variations in theophylline metabolism were found in five human subjects given 300 mg po (1569). For example, in two subjects, the concentration of drug plus metabolites excreted in the urine within 24 hr was 27.4 and 7.0 mg, respectively, while the 12-hr plasma levels were 10 and 2.3 mg/liter. Two major metabolites were identified as 1,3-dimethyluric acid and 3-methylxanthine. In a group

of hospitalized patients, most of whom smoked, the half-life of theophylline following 5 mg/kg iv was 3.6 hr (1570). In nonsmokers, the half-life was 7.2 hr; it was 4.1 hr for those who smoked. This difference was attributed to enzymatic induction in the smokers.

The serum half-life of propylthiouracil administered intravenously averaged 77 min in seven normal subjects (1571). The data conformed to a two-compartment model, and rate constants and elimination constants were calculated. The half-life of 200 mg of propylthiouracil administered orally was 1.1 hr (1572). Haloperidol was rapidly absorbed by normal subjects following intramuscular administration, with the maximum plasma level reached within 20 min (1573). The plasma level profile followed multicompartment model kinetics with a terminal elimination half-life of 20.7 hr. The prolonged elimination half-life suggested that a delay of 3–5 days occurred before equilibrium plasma levels are reestablished following a change in dosage regimen. Concomitant administration of vitamin C (ascorbic acid) was shown to alter the ratio of metabolic products of salicylamide excreted in the urine (1574). Although the sum of urinary excretion products was unaffected by vitamin C, glucuronide formation increased whereas sulfate conjugation decreased.

Antigen distribution and clearance were viewed as pharmacokinetic problems complicated by the intervention of the immune response (1575). A model characterizing the clearance of a simple antigen from the bloodstream of experimental animals, as well as the subsequent serum antibody response, was developed. Although it was envisioned that modification of the model would be required to explain more complex systems, early events in the immunological response were adequately accounted for in a consistent and quantitative manner. Blood levels and exhalation data from dogs and humans were used to elucidate a pharmacokinetic model describing the time course of trichloromonofluoromethane and dichlorodifluoromethane (1576). The model was used to estimate the percent of dose absorbed, which averaged 77% for trichloromonofluoromethane and 55% for dichlorodifluoromethane, and to predict their levels under various conditions simulating both short- and long-term exposure to maximum allowable concentrations.

Bioavailability of commercial carbamazepine tablets administered with and without meals was compared to that of a propylene glycol solution with respect to extent of absorption (1577). Although the drug was rapidly absorbed from the glycol solution, only 8% was absorbed from the commercial tablet. The data were consistent with dissolution rate-limited absorption. The fraction of dose absorbed and excreted in urine, the time of maximum serum concentration, and absorption and elimination half-lives appeared to be independent of dose.

In another study, an alcoholic solution of carbamazepine administered orally produced maximum plasma concentrations varying from 1 to 7 hr after dosing (1578, 1579). The half-life ranged from 24 to 46 hr and was dose independent. In patients subjected to multiple dosing, however, the plasma half-life decreased. The steady-state plasma concentration expected during multiple dosing was calculated from pharmacokinetic parameters obtained in single-dose studies. The results suggested that the drug induced its own metabolism.

In a comparative study of three penicillins, peak serum concentration and area under the serum concentration–time curve were greatest for amoxicillin followed by pivampicillin and then hetacillin (1580). The serum half-lives for amoxicillin and hetacillin were greater in nonfasting than in fasting subjects. Approximately 45% of the radioactivity given orally as ^{35}S-labeled phenoxymethyl penicillin (penicillin V) potassium was absorbed by the upper region of the GI tract (1581). In GI aspirates, ~10% of the drug was degraded to pencilloic acid. The cumulative recovery of intact drug in the urine was ~30% of the dose. The incomplete recovery was due to decomposition and poor absorption in the GI tract.

A two-compartment open model was developed to describe the absorption, distribution, metabolism, and excretion of cephapirin and its major metabolite, the desacetyl derivative, following intravenous and intramuscular administrations (1582). The model included metabolism in both plasma and the kidney. Clearance calculations and digital computer simulation supported the model.

The literature pertaining to the pharmacokinetics of cephalosporin antibiotics and their clinical use was reviewed (1583). Significant differences were shown to exist in the blood level–time profiles for the various dosage regimens of gentamicin recommended for patients with impaired renal function (1584). Although most methods achieved peak steady-state blood levels that exceeded the effective response concentration of 4 mg/ml, the percent duration of the dosing interval above and below minimal effective levels varied markedly for the various methods. Methods based on serum creatinine levels were considered to be less desirable than those using creatinine clearance as an index of renal function, since unduly long dosing intervals during moderate to severe renal impairment may be incorrectly employed. The recommendation was made that serum creatinine measurements be converted to creatinine clearance.

Clotrimazole was shown to be well absorbed orally and readily eliminated, mainly as an active metabolite in bile with only small quantities found in urine (1585). Peak plasma levels of sulfamethoxazole were reached in 2–4 hr by persons ingesting 800 mg alone or together with 160 mg of trimethoprim (1586). Simultaneous administration of trimethoprim did not affect the pharmacokinetics of sulfamethoxazole. An oral dose of 5 mg of isosorbide dinitrate was rapidly absorbed, biotransformed, and excreted in human subjects (1587). Peak whole blood concentrations of radioactivity were reached after 1.5–2 hr and declined relatively slowly. The radioactivity in whole blood was mainly represented by metabolic products. The metabolic products declined relatively slowly during 6 hr after oral dosing. Following oral administration of propoxyphene to children, peak blood levels were found after 2–3 hr with an apparent half-life of 4.8 hr (1588). A positive correlation was found between the plasma level of propoxyphene and norpropoxyphene, the major metabolic

Table XXXII—Additional References on Pharmacokinetics

Reference	Topic
1602	Absorption and metabolism of 7-chloro-3,3a-dihydro -2-methyl- 2*H*,9*H*-isoxazolo[3,2-*b*]-[1,3]benzoxazin-9-one
1603	Review of pharmacokinetics of flavinoids
1604	Pharmacokinetics of acetazolamide in glaucoma
1605	Plasma levels after single oral dose of proscillaridin
1606	Bioavailability of dioxidine and quinoxidine
1607	Review of metabolism of griseofulvin
1608	Review of pharmacokinetics of D-penicillamine
1609	Pharmacokinetics of haloperidol
1610	Review of pharmacokinetic function of pulmonary circulation
1611	Review of pharmacokinetics of inhalation anesthetic agents
1612	Absorption and elimination of clofazimine
1613	Bioavailability of clofazimine
1614	Pharmacokinetics of 1-(isopropylamino)-3-(2-methylindole-4-yloxy)-2-propanol (LF 17-895)
1615	Review of pharmacokinetics of pentazocine
1616	Review of pharmacokinetics of pentobarbital
1617	Pharmacokinetics of acetaminophen elimination in anephric patients
1618	Review of pharmacokinetics of frusemide (furosemide)
1619	Pharmacokinetics of indapamide
1620	Absorption, blood levels, and elimination of prothionamide
1621	Butylbiguanide concentrations in plasma, liver, and intestine after intravenous and oral administrations
1622	Review of pharmacokinetics of hypoglycemic agents
1623	Review of pharmacokinetics of tolbutamide
1624	Review of pharmacokinetics of sulfonylureas
1625	Pharmacokinetics of 4-amidinophenylpyruvic acid
1626	Influence of viral hepatitis on phenytoin pharmacokinetics
1627	Review of pharmacokinetics of heparin
1628	Effect of proadifen hydrochloride (SKF 525A) on pharmacokinetics of rifampicin (rifampin)
1629	Effect of phenobarbital on half-life of rifampicin
1630	Pharmacokinetics of cefoxitin and cephalothin
1631	Pharmacokinetics of cefazolin
1632	Review of pharmacokinetics of doxycycline
1633	Review of pharmacokinetics of minocycline
1634	Review of pharmacokinetics of amoxicillin
1635	Comparison of pharmacokinetics of a substituted penicillanic acid (BL-P1654) and ampicillin
1636	Pharmacokinetics of carbamazepine
1637	Pharmacokinetics of oxazepam and other benzodiazepines
1638	Pharmacokinetics of cytosine arabinoside (cytarabine) and pharmacokinetic simulation
1639	Blood digoxin levels
1640	Plasma concentrations of intravenous β-methyldigoxin (medigoxin)
1641	Plasma concentrations of diphenylhydantoin (phenytoin)
1642	Absorption and metabolism of pivampicillin
1643	Steady-state kinetics of penfluridol in psychiatric patients
1644	Absorption, metabolism, and excretion of naftidrofuryl (LS-121)
1645	Serum cephalosporin levels
1646	Review of pharmacokinetics of antineoplastic agents and immunosuppressants
1647	Blood levels in mother and child after oral administration of doxycycline antepartum
1648	Digoxin intoxication and plasma levels
1649	Review of pharmacokinetics of rifampicin
1650	Review of usefulness of blood levels of antiepileptic drugs
1651	Pharmacodynamics of 4-bromo-2,5-dimethoxyphenylisopropylamine
1652	Plasma half-life of cytosine arabinoside (cytarabine)
1653	Serum diazepam levels after repeated injections
1654	Distribution of labeled chlorpromazine
1655	Pharmacokinetics of maprotiline
1656	Pharmacokinetics of sulfaclomide and effect on *p*-aminohippuric acid clearance
1657, 1658	Review of pharmacokinetics of amoxicillin
1659	Disposition of acetylmethadol (methadyl acetate) in relation to pharmacological action
1660	Change in elimination half-life of aminophenazone (aminopyrine) in pregnancy
1661	Review of pathways of drug metabolism
1662	Review of drug distribution
1663	Review of drug metabolism
1664	Review of pharmacokinetic drug interactions
1665	Acetaminophen metabolism
1666	Metabolism of 2-(*p*-aminobenzoyloxy)benzoic acid
1667	Plasma levels and clinical effects of thioridazine and thiothixene
1668	Plasma levels and effects of antidepressants
1669	Relationship of clinical effect to digoxin concentration
1670	Disposition of *d*-propoxyphene
1671	Effect of diuretics on urinary excretion of cephalothin
1672	Acetanilide pharmacokinetics before and during diphenylhydantoin (phenytoin) administration
1673	Pharmacokinetics of amoxicillin
1674	Metabolism of cyproheptidine
1675	Comparison of blood levels with bupivacaine carbonate and hydrochloride
1676	Plasma levels of diftalone in rheumatoid arthritis
1677	Structural analysis of compartmental models for hepatic kinetics of drugs
1678	Review of pharmacokinetics of drug interactions
1679	Pharmacokinetic principles in chemical teratology
1680	Pharmacokinetic aspects of antibiotic therapy
1681	Pharmacokinetics of tranexamic acid
1682	Pharmacokinetics of radioiodine-labeled mercury compounds
1683	Pharmacokinetics of bucloxic acid
1684	Pharmacokinetics of methindione
1685	Blood trichloroethanol levels after oral administration of chloral hydrate
1686	Review of pharmacokinetics of nonsteroidal anti-inflammatory agents
1687	Pharmacokinetics of single oral dose of clofibrate
1688	Pharmacokinetics of ascorbic acid
1689	Pharmacokinetics in newborns and infants
1690	Plasma levels and urinary excretion of thiamphenicol in infants
1691	Review of absorption, metabolism, and excretion of drugs in geriatric patients
1692	Review of digoxin metabolism in geriatric patients
1693	Absorption, distribution, and excretion of labeled C-methyl ester of amphotericin B
1694	Blood levels and urinary excretion of *N*-(2-hydroxyethyl)cinnamamide
1695	Absorption and excretion of lactulose
1696	Review of pharmacokinetics of diphenylhydantoin (phenytoin)
1697	Review of pharmacokinetics of diphenylhydantoin in uremic patients
1698	Plasma concentrations of diphenylhydantoin and its metabolites
1699	Alteration of warfarin pharmacokinetics in an operating-room environment
1700	Pharmacokinetics of anticoagulant activity of coumarin drugs

(continued)

Table XXXII—*(Continued)*

Reference	Topic
1701	Pharmacokinetics of procainamide
1702	Pharmacokinetics of *N*-acetylated metabolite of procainamide
1703	Elimination of *N*-acetylprocainamide after intravenous dose of procainamide
1704	Influence of heart failure on blood levels of lidocaine and its monodeethylated metabolite
1705	Pharmacokinetic analysis of pharmacological effects and drug disposition of acetaminophen and 4-aminoantipyrine
1706	Pharmacokinetics of phenacetin
1707	Kinetics of salicylate elimination by anephric patients
1708	Kinetics of salicylates in blood and joint fluid
1709	Metabolism of secobarbital
1710	Pharmacokinetics of hexobarbital in humans after intravenous infusion
1711	Pharmacokinetics of hexobarbital in acute hepatitis
1712	Levels of morpethidine in maternal and fetal plasma following intramuscular administration of meperidine
1713	Pharmacokinetics of ^{3}H-4-acetylvinblastine
1714	Pharmacokinetics of guanazole
1715	Absorption, distribution, and excretion of alprenolol
1716	First-pass effect and dose-dependent availability of alprenolol
1717	Plasma concentrations and time course of β-adrenergic blockade due to propranolol
1718	Kinetics of propylthiouracil in hyperthyroidism
1719	Pharmacokinetics of disopyramide (Norpace)
1720	Pharmacokinetics of metronidazole
1721	Absorption and excretion of thioridazine and mesoridazine
1722	Pharmacokinetic determinants of response to single doses of chlordiazepoxide
1723	Effects of age and liver disease on disposition and elimination of diazepam
1724	Pharmacokinetics of chlorprothixene
1725	Pharmacokinetics of transfer of ampicillin to amniotic fluid
1726	Blood, urine, and bile levels of ampicillin after continuous infusion
1727	Pharmacokinetic studies with mecillinam and pivmecillinam
1728	Clinical pharmacokinetics of ticarcillin and carbenicillin
1729	Pharmacokinetics of sulbenicillin
1730	Pharmacokinetics of transfer of cephalothin into amniotic fluid
1731	Pharmacokinetics of cefazolin
1732	Adjustment of cephaloridine dosage according to its pharmacokinetics
1733	Gentamicin blood level–time profiles of various dosage regimens in renal impairment
1734	Unaltered metabolism of antipyrine and tolbutamide in fasting man
1735	Measurement of plasma concentrations of tolbutamide by GLC
1736	Pharmacokinetics of floctafenine
1737	Pharmacokinetics of flucytosine in cryptococcal meningitis
1738	Pharmacokinetics of clofibrate and chlorophenoxyisobutyric acid
1739	Monitoring of plasma levels of halofenate
1740	Pharmacokinetic studies with radioactive *N*-propylajmalinium hydrogen tartrate
1741	Comparative pharmacokinetic studies of ornidazole and metronidazole
1742	Fate of emepronium in humans in relation to its effect
1743	Pharmacokinetics of pindolol
1744	Pharmacokinetics of magnesium
1745	Pharmacokinetics of viloxazine
1746	Blood levels of bupivacaine in obstetric analgesia
1747	Cerebrospinal fluid concentrations of diazepam and its metabolites
1748	Methaqualone in serum and cerebrospinal fluid after oral intake
1749	Plasma concentrations and effects of methaqualone after single and multiple oral doses
1750	Relationship between behavioral effects and plasma levels of amantadine
1751	Pharmacokinetics of ifosfamide
1752	Pharmacokinetics of saralasin in hypertensive patients
1753	Pharmacokinetics and metabolism of glycinexylidide
1754	Effect of etiocholanolone-induced fever on plasma antipyrine half-life
1755	Pharmacokinetic data and drug monitoring: antibiotics and antiarrhythmics
1756	Pharmacokinetics rational for sulfadoxine–pyrimethamine mixture administered once monthly for malarial suppression
1757	Pharmacokinetics of bethanidine in hypertensive patients
1758	Pharmacokinetics of 5,6-*trans*-25-hydroxycholecalciferol
1759	Pharmacokinetics of tinidazole and metronidazole in women after single large oral doses
1760	Pharmacokinetics of rimiterol
1761	Pharmacokinetics of chlormethiazole
1762	Prediction of steady-state plasma levels of nortriptyline from single oral dose kinetics
1763	Pharmacokinetics of drugs in patients with nephrotic syndrome
1764	Carbenicillin therapy in patients with normal and impaired renal function
1765	Plasma concentrations of pancuronium bromide in patients with normal and impaired renal function
1766	Pharmacokinetics of doxycycline in patients with normal and diseased kidneys
1767	Minocycline excretion and distribution in relation to renal function
1768	Pharmacokinetics and dosage of dextran 40 in relation to renal function
1769	Disappearance of phenazone (antipyrine) from plasma in patients with obstructive jaundice
1770	Pharmacokinetics of thiamphenicol in normal and renal insufficiency subjects
1771	Changes in blood thiamphenicol levels in renal failure
1772	Serum levels of thiamphenicol in patients with impaired liver and kidney function
1773	Pharmacokinetics of terbuclomine in renal insufficiency
1774	Lithium elimination as a function of age in normal and renal insufficiency subjects
1775	Pharmacokinetics of clindamycin in normal subjects and renal failure patients
1776	Pharmacokinetics and metabolism of lidocaine in patients with renal failure
1777	Plasma levels of lidocaine during treatment with phenytoin and procainamide
1778	Pharmacokinetics of acetanilide and diphenylhydantoin (phenytoin)
1779	Metabolism and disposition of labeled hydralazine
1780	Pharmacokinetics of actinomycin D (dactinomycin) in patients with malignant melanoma
1781	Acetylation of procainamide and its relationship to isonicotinic acid hydrazide (isoniazid) acetylation phenotype
1782	Polymorphic acetylation of procainamide

product. The first-pass liver metabolism, as well as variation in the half-life, was suggested as being responsible for changes in the amount of available propoxyphene.

Plasma levels of dexamethasone phosphate and free alcohol were determined following intravenous ad-

ministration of the phosphate (1589). Areas under the plasma dexamethasone alcohol curves were a linear function of the phosphate dosage over a 40-fold range, and an overall conversion of phosphate to alcohol of 90% was indicated. A first-order rate conversion constant of 4.03 hr^{-1} was approximately 25 times that for hydrolysis in whole blood incubated *in vitro*. The results suggested that the major component of phosphate hydrolysis occurs within highly perfused organs comprising the central kinetic compartment. A large first-pass effect was evident, with about 50% of orally administered diphenhydramine being metabolized by the liver before reaching general circulation (1590). The drug administered in solution appeared to be fully available to the hepatoportal system. Cumulative amounts of unchanged drug excreted in the urine were less than 4% of the administered dose.

Theoretical equations were derived to estimate the extent of the hepatic and pulmonary first-pass effect after oral and intraperitoneal administrations (1591). Calculations using data from two normal adult subjects suggest that the fractions of chloroform metabolized in the liver and excreted intact from the lung in the first pass are maximally 0.38 and 0.172, respectively. Close agreement between predicted and experimental values for the pulmonary excretion clearance also was found. The pharmacokinetics of tolmetin studied after oral administration showed that the data were capable of being fitted to a one-compartment open model (1592). An overall mean elimination rate constant of 0.839 hr^{-1}, corresponding to a plasma half-life of 0.83 hr, was obtained in the 12 subjects studied. Similar results were seen after multiple dosing in arthritic patients.

Approximately one-third of a single therapeutic dose of phenformin administered to two healthy volunteers was excreted unchanged in the urine over a 4-day period subsequent to dosing (1593). Profiles were obtained for urinary excretion rates and plasma and saliva concentrations. The terminal exponential decline indicated a half-life of approximately 11 hr. A one-compartment model was proposed to describe the pharmacokinetics of creatinine in humans (1594). The average biological half-life in normal male adults between 20 and 39 years was 3.85 hr and was prolonged in patients with renal dysfunction to up to 77 hr when renal function decreased to 5% of normal. The use of a pharmacokinetic approach to interpret serum creatinine levels in patients suffering from renal failure was recommended. Plasma and saliva concentrations of isoniazid were determined following oral administration to two slow acetylator subjects (1595). The results indicated that salivary levels provide a useful approach for acetylation phenotyping. A report reviewed recent publications dealing with the study of pharmacokinetics in the aged population (1596). The rate and extent of drug absorption do not appear to be altered to an appreciable degree in elderly patients. However, drug disposition may be affected by a number of factors, including alterations in protein binding, apparent volumes of distribution, and renal and/or extrarenal clearance of drug.

The plasma half-life of diphenylhydantoin (phenytoin) in newborn infants of epileptic mothers treated with the drug was shown to be in the same range as the plasma half-life in adults (1597). Rapid metabolism and plasma disappearance of the drug were demonstrated. In newborn children whose mothers had been given phenobarbital, the blood plasma half-lives ranged from 77 to 404 hr and were inversely correlated with the extent of prenatal exposure to the drug (1598). In three infants, a biphasic plasma curve was found in which there was a sudden change from slow to fast disappearance of drug on the 5th–7th day of life.

A study of the distribution and elimination of lidocaine and mepivacaine in subjects after obstetric epidural anesthesia showed that epinephrine significantly lowered the concentrations of the anesthetics in the mothers' circulations (1599). However, epinephrine significantly increased the concentrations of the anesthetics found in the newborn's circulation at delivery. Of importance was the long persistence of the anesthetics in the infant's circulation.

Amoxicillin absorption was similar in normal subjects, pernicious anemia patients, and patients with renal failure (1600). Therapeutic levels were reached in the serum and urine of patients with creatinine clearance levels below 10 ml/min. The half-life was increased markedly in patients undergoing dialysis therapy. A one-compartment model designed to predict alterations in persistence of drugs in uremic patients was constructed using information obtained from normal subjects, and predictions were made for 22 drugs (1601). Terminal half-lives, percent excreted unchanged, and reported changes in half-life associated with decreased renal and hepatic functions were tabulated for 186 drugs studied in humans. References were obtained from 332 original articles which were critically evaluated in this study.

Additional references on pharmacokinetics are listed in Table XXXII.

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