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A Literature Review

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CONTENTS

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PHARMACEUTICAL CHEMISTRY

IN 1963, PROGRESS of the chemical aspects of pharmaceutical science was reviewed in several publications. New products released during 1962 were the topic of reviews by deHaen (599) and Tice (600). It was pointed out that the new chemical entities released by the American drug industry in 1962 were fewer than in any year of the last decade. Another writer cited 449 references in a survey of the research progress in synthetic medicinals and natural substances in 1961 (601). Bucher also reviewed new developments in pharmaceutical chemistry with examples of products marketed in Germany (602). Problems of drug research were the theme of another report (603). Sources of potential drugs were treated in other publications (604–606).

Pharmaceutical applications of azulenes (607) and antitussives (608) have been analyzed. The synthesis, properties, and uses of some new barbiturates were described (609). Vitamins and amino acids in the Japanese pharmaceutical industry were discussed in a paper on pharmaceutical nutritive preparations (610). Blazek reviewed

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phenothiazine derivatives in pharmacy (611), and Petrow surveyed steroid progress for the year 1962 (612). Consideration of the potential of enzymes for topical application also appeared in the literature during 1963 (613). In another article, the chemistry, pharmacology, and pharmacy of gold compounds were reported (614). A summary on stereochemistry with pharmaceutical illustrations was published (615); 74 references were cited.

The composition of spermaceti (616) and montan wax (617) has been determined. Christie, *et al.*, elucidated the structure of butolic acid, a hydrolytic product of shellac resin (618). Some low-boiling constituents of peppermint oil were investigated by McCarthy, *et al.* (619). A review of separation methods, structure, and uses of glycyrrhizic acid and its derivatives was published (620). The preparation of tocopherol concentrates from wheat germ by three different methods (621), and the isolation and crystallization of human insulin (622) have been reported.

David, *et al.*, noted the physicochemical characteristics of some important sulfonamide derivatives (623), and Garrett dealt extensively with the physical chemistry of complex transformations of the antibiotic, porfiromycin (624). An investigation of the stereochemistry of cycloheximide and its degradation products was printed (625). In a paper on the stereochemistry of steroids, hydrogenation of 11β-hydroxy-Δ^8-dehydroestrone was described (626). Three articles on antacids were found: Eriksen, *et al.*, investigated the antacid properties of calcium, magnesium, and aluminum salts of water-insoluble aliphatic acids (627); in another paper, the acid-neutralizing velocity of synthetic aluminum silicate and dried aluminum hydroxide gel was studied (628); the third publication was concerned with critical *in vitro* factors in the evaluation of gastric antacids (629). Mirimanoff, *et al.*, reported on the salt formation between theophylline and phenylmercuric hydroxide (630). Solution phase interaction between nicotinamide and ascorbic acid was examined by Guttman and Brooke (631). A liquid-liquid extraction method for concentration of aqueous solutions has also been described (632). The elution of vitamin B_{12} from carbon cake was considered by Kosaka (633).

Polymers.—The chemical and physical properties of polymers and their applications in pharmacy have been reviewed by Allisson (634) and Autian (635, 636). Studies of the interactions between polyvinyl alcohol and procaine hydrochloride (637), low molecular weight compounds and solid polymers (638), and polar aromatic molecules with neutral polymers and polyanions (639) were reported. The use of various water-soluble copolymers to form salts with penicillins was examined (640). Research on theoretical aspects of polymer association and hydrogen bonding has been conducted (641). Polymer-solvent interaction in polymer solutions was also noted (642). Phase equilibria for a polymer-solvent-nonsolvent system were presented by Nakagaki and Sunada (643). In another paper the acid behavior of carboxymethylcellulose was disclosed (644).

Maurer investigated particle-size distribution in polymer solutions (645). The effect of irradiation on the change in molecular weight distribution in polymers was described (646). In another publication a kinetic study of gelatin cross-linking by formaldehyde and glyoxal was revealed (647). Filtration of silica dispersions flocculated by high polymers was studied (648). Hermans reported a method for derivation of the molecular weight distribution of a polymer system from the sedimentation equilibrium (649). Also published was a procedure for the determination of sedimentation coefficients in rapidly equilibrating polymerizing systems (650).

Antibiotics.—Two general reviews of antibiotics with several references were published (651, 652). During 1963 the tetracycline antibiotics were reviewed in four different publications (653–656); these publications, citing many references, included the history, chemistry, pharmacy, and pharmacology of these drugs. New developments in the penicillins were discussed by Lhoest (657); and Uri reviewed the cephalosporins, antibiotics similar in structure to penicillin (658). A new iron-containing antibiotic, succinimycin, was reported by Haskell, *et al.* (659). Other new antibiotics disclosed in the literature last year were cirramycin (660) and monazomycin (661). Sugawara, *et al.* (662), and Sugawara (663) presented studies on protomycin, a new antibiotic of the cycloheximide group which is active against *Endameba histolytica.*

Leeson, *et al.*, recorded the thermodynamic pKa values for the three dissociation constants of three different tetracycline molecules (664). The variation of pKa′ values of tetracyclines in dimethylformamide-water solvents was also investigated (665). The crystal structure of chlortetracycline hydrochloride was confirmed (666), and the identity of cephalothin sodium was established through crystallography (667).

Huber, *et al.*, examined variation in capacity of batches of corn-steep liquor to enhance the microbiological yields of antibiotics and cyanocobalamins (668). Another article was concerned

with the manufacture of five new semisynthetic penicillins (669). Purification of cephalomycin by isoelectric precipitation and gel filtration was reported (670). The freeze-thaw method was applied for concentration of antibiotic solutions (671). Samsonov and Fleer presented a method to separate and purify erythromycin with cation-exchange resins (672), and penicillin adsorption on ion-exchange resins was the topic of two papers by Samsonov, *et al.* (673, 674). Other researchers investigated the adsorption of streptomycin from aqueous methanol solutions by carboxylic cation exchangers (675).

Radioisotopes.—Johnson, *et al.*, reviewed some applications of radioisotopes in the chemical industry (676), and Snell discussed the use of tritium-labeled compounds in pharmaceutical research (677). Another review dealt with the effects of ionizing radiation on pharmaceuticals (678). Effects of gamma-rays on aqueous solutions of *p*-aminobenzoic acid (679) and on gelation of dilute aqueous pectin solutions (680) were investigated. It has been found that radiation decomposes anion-exchange resins (681). Cornish studied ionization distribution in water irradiated with fast electrons using glass as a radiation indicator (682). One writer reviewed the potential of radio-sterilization in the pharmaceutical industry (683), and another worker explored its application to various antibiotics in ophthalmic ointment bases using Co^{60} (684). Some effects of sterilizing doses of radiation on ophthalmic solution ingredients have also been investigated (685). Clark and Swartz applied radioisotopes to research on absorption in pharmaceutical closures (686).

The use of tagged elements in the newly developed field of medical experimentation was reviewed (687). Ingrand discussed the contribution of radioisotopes to the pharmacodynamic study of proteins and polypeptides (688). Radioisotopes were also used to establish arginine as the precursor of galegine in *Galega officinalis* (689). Another paper dealt with the potential use of radioactive vitamin B_{12} as a gastrointestinal dilution indicator (690). A description was given for the preparation of radiochemicals and their formulation into parenteral dosage forms (691). Also reported was the preparation of colloidal chromic phosphate (P^{32}) for medical use (692).

Armstrong, *et al.*, proposed a tissue-equivalent chemical dosimeter capable of measuring ionizing radiation doses as low as 500 millirad (693). Methodology for simultaneous determination of H^3 and S^{35} in samples with variable quenching was disclosed (694). Another author found a linear relationship between optical density and quenching of liquid scintillation samples (695). Medium-density polyethylene vials have been compared with glass vials for use in liquid scintillation counting; lower backgrounds and increased efficiencies were observed with plastic vials (696). New techniques in 4π β-counting were presented in two papers (697, 698). Blanchard reported a computer program for automated testing and reduction of liquid scintillation counting data (699). An investigation of *in vivo* tracer techniques in drug screening studies was conducted by Rupe, *et al.* (700). Techniques and equipment for measuring total body radiation were also described in another paper (701). Various methods for the detection of radioisotopes in urine have been examined (702, 703).

BIOPHARMACEUTICS

Biopharmaceutics comprises the research effort directed toward studying the influence of pharmaceutical formulations on biological activity of medicinals. Experimental work in this area necessitates the application of knowledge evolving from other disciplines such as physical chemistry, physiology, and biochemistry. The numerous references presented here are indicative of continued interest and progress in this field.

Mechanisms of drug action appeared to be an area of experimental activity in 1963. Two publications were concerned with the dynamics (704) and chemical models (705) of drug-receptor interaction. A flux-carrier hypothesis was proposed to combine some features of the receptor theory with other features of the potential theory (706). Beckett and Youssef considered active sites in stereoselective adsorbents as drug-receptor models (707), while charge transfer, hydrogen bonding, and drug action were dealt with in a paper by Nash and Allison (708). Additional research was reported on the transport of ions across membranes in a static system (709).

Clinical evaluation of pharmacologically active compounds was the subject of a review; it was pointed out that as new techniques are developed the science of clinical evaluation will become more precise (710). In a seminar on the clinical evaluation of drugs, Ruemke discussed some of the applications of statistics to a wide variety of clinical trials (711). A generalized kinetic regression analysis, hypergeometric kinetics, was proposed for empirical curve fitting or estimating parameters of biological significance (712). An analysis of species differences and individual variations in drug metabolism was also reviewed (713).

Several researchers have observed the effects of alkali (714) and ACTH (715) on gastric secretion. Rune and Koster reported the use of a dialysis bag *in situ* for measuring gastric acidity (716). Another paper, by Nordgren, described the rate of secretion and the electrolyte content of normal gastric juice (717). A preliminary report was made on the separation of pepsins from human gastric juice (718).

Clinical significance of hydrogen-ion concentration in the duodenum was ascertained; duodenal pH was found to be influenced largely by the acidity of the stomach (719). Investigation of intestinal sensitivity to gastric juice was also conducted (720). Hunt studied the duodenal regulation of gastric emptying—the pattern of gastric emptying was found to be exponential and controlled by receptors responding to carbohydrates, osmotic pressure, and acid (721). Connell, *et al.*, used miniature radio transmitters enclosed in capsules for studying pressure of the intestinal tract during motility (722). Paper electrophoresis was employed to identify known and unknown components of pancreatic juice (723). A study of 12 enzyme systems in the mucosa of the normal human gastrointestinal tract was published (724). Dubos, *et al.*, discussed the composition, alteration, and effects of intestinal flora (725).

Current knowledge of visceral blood flow has been surveyed (726). Publications by Jacobson (727), Texter (728), and Welsh (729) were concerned with gastric blood flow, small intestinal blood flow, and colon blood flow, respectively. Blood circulation time in dogs of different ages was measured by other investigators (730).

It has been suggested that bile acids facilitate absorption of lipids by virtue of their ability to form micelles which solubilize the products of lipolysis (731). Roe pointed out a need for extensive research on the influence of food on drug absorption from the intestinal tract (732). The action of chloramphenicol on the coefficient of absorption of *p*-aminohippuric acid in man and rabbits was discussed (733). From *in vivo* studies on protein digestion, it was reported that pepsin predigestion is important to the rate of disappearance of vegetable proteins (734). Davies commented on the effect of sodium salts of organic acids on urinary pH (735).

Effects of Physicochemical Properties.—Linford observed the influence of pH on the reactivity of chlorambucil (736); the effect of pH on membrane permeability was discussed by Ariens and Simonis in relation to pH and drug action (737). In a review article, the influence of hydrogen-ion concentration on ophthalmic solutions, disinfectants, mold-inhibiting agents, antibiotics, and the control of urine pH was summarized (738).

Diffusion of organic electrolytes in hydrogen-bonding systems has been investigated (739). McGowan discussed partition coefficients and biological activity (740), and Leonards found the rate of gastrointestinal absorption of aspirin to be markedly influenced by the drug's solubility (741). The efficiency of absorption of several cetyl sulfate salts of drugs was evaluated (742). In a study of 40 dextran samples it was ascertained that renal excretion was dependent on molecular weight, regardless of the method of preparation of the dextran sample (743). Insulin binding properties in human serum were studied by a combination of immuno-electrophoresis and autoradiography (744). Calcium binding compounds were found to increase the gastrointestinal absorption of heparin (745). Interactions of steroids with human plasma proteins were reported by Slaunwhite, *et al.* (746).

Effects of Formulation.—Morrison and Campbell presented a review article on physiological availability of drugs in oral dosage forms (747). Their discussion of various types of formula modifications included sugar coatings, enteric coatings, and prolonged-release products. The effect of dosage form on biological activity was the subject of another publication (748). Two papers by Walker and Kennedy dealt with the physiology of the skin as applied to formulation (749) and factors influencing the rate and extent of percutaneous absorption from various dosage forms (750). The permeability of excised human keratin to lipid-soluble substances (751) and the absorption of phenylbutazone ointment through the skin of rats and humans (752) were examined. Cascorbi studied emulsified anesthetics for intravenous injection, finding that high potency and high boiling point are required for the most satisfactory preparations (753). Clinical trial of a new aerosol dosage spray for nasal application was described in another paper (754). Two references were found which dealt with absorption of sulfonamides and their sodium salts from various suppository bases (755, 756). Glycerinated gelatin was proposed as a base for prolonged-action vaginal suppositories (757).

An *in vivo* method for the determination of disintegration time of orally administered medicinals was reported (758). Urinary excretion in humans was employed to analyze the disintegration of protective-coated tablets (759). Sunkes studied the effect of selected granulating agents on the release of medication from granules—both *in vitro* and *in vivo* methods were used (760).

Spironolactone blood and urine levels were compared after administration of micronized powder with a surfactant and tablets (761). In a review article, Lees discussed the influence of clinical and pharmaceutical aspects of fine particles on drug absorption; preparation of powders, tablets, and suspensions; drug solubility and stability; and manufacturing, milling, and polymorphism (762). Levy also considered the effects of particle size on dissolution and gastrointestinal absorption rates of pharmaceuticals (763).

Pharmaceutical aspects of a *p*-aminosalicylate–dialdehyde starch compound were studied by Campbell (764). Aspirin-caseinate was found to be effective and less irritating to patients with gastric sensitivity to plain aspirin (765). The effect of some antispastic drugs on the absorption of antituberculosis inhalation preparations was reported (766). Poole and Gardocki investigated the prolongation of chlorzoxazone plasma levels in mice and dogs by zoxazolamine (767). Adams explored the effect of drugs and differing routes of administration on the urinary excretion of parenteral vitamin B_{12} (768). Corneal permeation rate and length of action of ophthalmic ointments with dissolved and crystalline chloramphenicol were examined (769). The influence of stearic acid on penicillin levels in blood after oral administration was also observed (770). Kharizanova noted the effects of certain vitamins on serum levels of some tetracyclines and penicillin (771). The individual contribution of sodium tartrate and tartaric acid to blood levels of tetracycline hydrochloride was investigated (772, 773).

Absorption Control.—Numerous references are included in several reviews of sustained-release dosage forms. Speiser (774), Peters (775, 776), and Simoons (777) discussed various factors in the development of sustained-release dosage forms—passive diffusion, methods of obtaining sustained release of medication, and problems in evaluating this type of dosage form were mentioned. In another review, Eriksen considered some of the specific constants describing absorption, distribution, and excretion of drugs as they apply to sustained-release medication (778). A dissertation on the theoretical aspects of prolonged-action drugs in tablet form was presented (779). Nelson analyzed some of the problems complicating evaluation and usefulness of delayed-action pharmaceuticals (780).

Rosen reported on the relationship of *in vitro* release to human urinary recovery for a sustained-release preparation of S^{35}-prochlorperazine (781). Oral prolonged-action products of penicillin (782) and ephedrine and chlorpheniramine (783), based on reaction or complexation with ion-exchange resins, have been prepared and investigated. Partial insolubilization of gelatin with formaldehyde was proposed as a basis for development of sustained-release products (784). Wynn and Landon studied the alimentary absorption of some enteric-coated sodium and potassium chloride tablets (785). Three papers published on the absorption of iron dealt with utilization of iron from a controlled-release dosage form (786), iron absorption in mice as modified by various agents (787), and regulation of intestinal iron absorption (788).

The evaluation of a long-acting, oral, antihistaminic decongestant for nasal allergies was reported (789). A double-blind, controlled study was used to compare slow-release and regular forms of thioridazine (790). Serum levels and clinical effects were observed in a comparative study of pentobarbital sodium in prolonged-action and conventional dosage forms (791). An evaluation of a long-acting oral preparation of methyl prednisolone was published (792), and Cavallito, *et al.*, employed urinary excretion in studying a sustained-release principle (793).

Oldham has presented a review on the chemical modification of sulfonylureas and related materials, including the development of long-acting sulfonamides (794, 795). Another discussion of sulfonamides dealt with rapid-acting, slow-absorbable, long-acting, and various addition products; several forms of penicillin were also discussed (796). Ballard and Nelson have investigated absorption and excretion of sulfadiazine after subcutaneous implantation of disks in rats (797).

The use of drugs as inhibitors of drug metabolism was reviewed (798). It has been found that the administration of a xanthine oxidase inhibitor concurrently with 6-mercaptopurine resulted in a marked decrease in metabolic oxidation of the latter *in vivo* (799). Other studies revealed the effects of a metabolic inhibitor, SKF 525-A, on metabolic rates of various drugs (800, 801). Oral hexobarbital, in the presence of *p*-aminosalicylic acid, increased sleeping time due to decreased elimination (802). Ruemke investigated the influence of several drugs on duration of hexobarbital and hydroxydione narcosis (803), and Kato, *et al.*, studied the mechanism of potentiation of barbiturates and meprobamate by imipramine (804). The influence of dextran for sustaining the action of orally administered drugs was evaluated (805). Increased streptomycin levels in rat skeletal muscle tissue were observed after administration of neostigmine methylsulfate alone and in combination with atropine (806).

Absorption Mechanisms.—A technique for making dose-response curves and their use in evaluation of drug parameters were described in two papers (807, 808). Hunt explored the relationship of gastric-emptying rate to drug absorption (809). Several references were cited in a review of the passage of drugs across body membranes (810). Another review was published about the physiology, biochemistry, and energetics of active transport (811). Ghosh also commented on active-transport and energy-transfer mechanisms (812), and Wilbrandt described active transport through interfaces (813). A model for permeation of living membranes was proposed by Shanes (814). Clearance experiments at different urine pH values were used to demonstrate the importance of pH-dependent diffusion processes for kidney function (815). Molecular size and the transfer of substances through the partition of blood capillaries were discussed by another writer (816). Parsons quantitated some aspects of pinocytosis in relation to intestinal absorption (817). The question of penetration through pores was considered in relation to the passive permeability of cell membranes (818). A study of the route and rate of absorption of inhaled vapors was published (819).

Active transport of quaternary ammonium compounds into bile was investigated by Schanker and Solomon (820). In another paper, Schanker, *et al.*, demonstrated the interaction of purines with the pyrimidine transport process of the small intestine (821). Chelation by lactose was suggested as a possible mechanism for enhancing intestinal absorption of calcium (822). Other researchers studied the development of mechanisms for intestinal absorption of vitamin B_{12} in growing rats (823). Vitamin B_{12} binding capacity of saliva and gastric secretions has also been ascertained (824).

Wilson reviewed principles concerned with percutaneous absorption (825), and Carson and Goldhamer described a tracer procedure for studying skin absorption (826). Percutaneous absorption of various animal or vegetable oils has been investigated (827). *In vitro* techniques were employed in an exploration of the effect of temperature and humidity on penetration of C^{14}-acetylsalicylic acid in excised human skin (828). Swelling response of skin disks was used to measure the effects of aqueous anionic, cationic, and nonionic surfactant solutions on human and calf skin (829). The influence of some surfactants on the cutaneous absorption of potassium iodide, sodium salicylate, and ammonium thiocyanate has also been examined (830).

Kinetic Studies.—The application of a newly derived composite radiocalcium reference standard in normal calcium kinetics was reported (831). Two papers were published describing the use of doubly labeled iron in evaluating the kinetics of iron absorption and metabolism (832, 833). By means of a steady-state perfusion technique, the longitudinal absorption gradient of L-methionine absorption was shown to decline progressively in the normal human small intestine (834). Andersen has stated that the rate of elimination of isonicotinic acid hydrazide in humans was proportional to plasma concentration (835). A presentation was made of the comparative pharmacodynamics, urinary excretion, and half-life determinations of nitrofurantoin sodium (836). Garrett, *et al.*, used an analog computer to examine the kinetics of steroid effects on Ca^{47} dynamics in dogs (837). Metabolism of acetaminophen by humans was the subject of another pharmacokinetic study (838). Nelson and Levy commented on the relationship of plasma salicylate concentration to urinary salicylate excretion rate observed at an elevated urinary pH (839).

A mathematical model of drug distribution and the solution of differential-difference equations have been reported (840). Higuchi analyzed the rate of release of solid drugs randomly dispersed in solid matrices (841). Kinetic studies and human metabolism and excretion of drugs from various dosage forms were reviewed (842). The subject of multiple-dose excretion kinetics was investigated by Wiegand, *et al.* (843)—general mathematical equations describing expected blood and urine drug concentrations were derived. Another manuscript on the theory of drug action disclosed the mathematics of dosage transfer (844). Mathematical models were used to determine the nature and extent of effect of experimental procedures on analysis of reaction curves (845). Per cent absorbed–time plots derived from blood level and/or urinary excretion data were presented by Wagner and Nelson (846). Wagner also discussed some possible errors in the plotting and interpretation of semilog plots of blood level and urinary excretion data (847). The validity of polynomial approximations in urinary excretion-rate studies was discussed in another paper (848); biological half-life and tissue concentrations were the subject of a presentation by Swintosky (849). The excretion and accrual of drug metabolites have also been considered (850).

Drug Absorption: Antibiotics.—In a review and discussion of the mechanisms of action of antibiotics, 246 references were cited (851). Sureau investigated variations in blood levels of

different antibiotics as a function of route of administration and the vehicle used (852). Single-disk and tube-dilution techniques for determining antibiotic sensitivities of Gram-negative pathogens were compared (853).

Blood levels and urinary excretion of some soluble esters of chloramphenicol in rat and man were reported (854). Distribution and excretion patterns were analyzed after oral administration of griseofulvin to rats (855). Karasaki and Matsubara found that trichomycin given orally to rabbits was rapidly decomposed by gastric acid (856). Various types and quantities of adsorbents were used in a study of the absorption of biomycin from the gastrointestinal tract of the chicken (857). The effect of orally and parenterally administered neomycin on plasma lipids of humans was the subject of another monograph (858). Two publications dealt with various aspects of malabsorption produced by neomycin (859, 860).

Tetracycline derivatives were evaluated by studying excretion and distribution in body fluids after intravenous administration to dogs; the relationship between serum concentration and lipid solubility was discussed (861). Using a new method for determination of tetracycline in urine, Kakemi, *et al.*, found the biological half-life of tetracycline to be about 8 hours (862). Another paper by Kakemi, *et al.*, reported some investigations of the absorption of tetracycline from the gastrointestinal tract (863). *In vitro* data were presented which support the theory that *in vivo* retention of tetracycline is due to calcium binding (864).

Single oral-dose blood levels of four phenoxypenicillins were compared with *in vitro* antibacterial activity (865). Absorption from the gastrointestinal tract of humans and *in vitro* activity against Gram-positive cocci were reported in studies with sodium diphenicillin (866). An investigation was published on the absorption, metabolism, and excretion of a new semisynthetic penicillin, 6-(2-ethoxy-1-naphthamido)-penicillanic acid (867, 868). Penicillinase interaction was considered in a discussion of chemotherapeutic aspects of penicillin (869). Smith and Hamilton-Miller commented on the differences between penicillinases from Gram-positive and Gram-negative bacteria (870). In an investigation of a new sulfonamide-penicillin combination, 5-methylsulfadiazine was reported to inhibit penicillinase (871). Papapanos, *et al.*, concluded that solution pH controlled the permeation of penicillins V and G into rabbit eyes (872). These authors also discussed the influence of blood concentrations on the diffusion of penicillins into the aqueous and vitreous humors of the human eye (873).

Drug Absorption: Inorganic.—Brown, in a review, noted the lack of agreement concerning both the precise mechanism and the regulation factors for iron absorption (874). Various aspects of iron therapy—including dosage forms, absorption, and mode of administration—have been disclosed (875). Another experiment showed decreased iron absorption in healthy aged humans (876). In two reports of mechanisms of iron absorption, Brown and Rother studied iron uptake by the normal rat and the influence of iron deficiency and other conditions on iron uptake by rats (877, 878). The role of transferrin in iron absorption has been evaluated (879), and radioactive iron (Fe^{59}) was used to study absorption of iron from the human large intestine (880). In a study of histamine-fast achlorhydria and iron absorption, it was found that Fe^{59} was absorbed three times greater in patients with acid gastric fluid (881).

Several papers were evident concerning the influence of various agents on the absorption of iron. Cleton, *et al.*, determined the influence of synthetic chelating agents on iron metabolism (882). An isolated-loop technique was used in studying absorption, distribution, and the effects of various chelating agents on radioiron in rats (883). Princeps has reported on the influence of the calcium disodium salt of ethylenediaminetetraacetic acid on iron metabolism (884), and Masuhara and Migicovsky noted the influence of vitamin D on the intestinal absorption of iron and cobalt (885). A dissertation on the influence of salicylate administration in iron metabolism was also published (886). Other investigators studied the effect of reducing agents on the absorption of iron (887).

Experiments by Code, *et al.*, were concerned with the influence of acid on the gastric absorption of water, sodium, and potassium (888). The gastrointestinal absorption of radioactive magnesium in the rat has been examined (889). Another paper disclosed a quantitative relationship between the absorption of calcium and phosphorous (890). Akagi, *et al.*, investigated variation of boron and phosphorus levels in some organs after oral administration of a single dose of borate (891).

Drug Absorption: Organic.—Schedl and Clifton found that absorption of cortisol from Ringer's solution in the normal human gut was characterized by a distally decreasing gradient (892). The absorption of castor oil in man was inversely related to the size of the dose (893). In a toxicological investigation of a potential

missile propellant, the absorption, distribution, and excretion of 1,1-dimethylhydrazine were investigated (894). Franc, *et al.*, determined absorption, distribution in tissues, and excretion after oral administration of buthiopurine-S^{35} to mice (895). Borzelleca stated that the absorption rate of nicotine from the urinary tract of the rat was dependent on solution concentration and pH (896). Additional research was reported on the absorption of hydrocortisone from the large bowel (897), of procaine from the gastrointestinal tract (898), of paracetamol tablets (899), and of chlorhydroxyquinoline (900).

Emmerson and Miya reviewed the metabolism of phenothiazine drugs (901). In a metabolic study of secobarbital, two main metabolites were isolated in addition to unchanged secobarbital (902). McMahon, *et al.*, studied the metabolism of nortriptyline-*N*-methyl-C^{14} in rats; this drug was found to be slowly, but effectively, absorbed from the intestinal tract (903). The metabolic fate of 5-cyclohexenyl-5-alkylhydantoins was discussed in a paper on the biotransformation of drugs having a cyclohexene ring (904).

The distribution and excretion of dichlorpromazine-S^{35} were studied following doses to rats and rabbits (905); the excretion and metabolism of S^{35}-labeled thioridazine in urine, blood, bile, and feces were described in another paper (906). Radioactive nicotine was used in a distribution and excretion study in various animals (907). The urinary excretion of benzquinamide in humans was reported by Cahn, *et al.* (908). Research on the elimination of glutethimide and long-acting barbiturates after toxic and therapeutically active doses was published (909).

Nogami, *et al.*, used the perfusion method to study effects of solution pH on the *in vivo* disappearance rate of sulfonamides from the rat small intestine (910). Idiopathic ulcerative colitis did not affect rectosigmoidal absorption of phenolsulfonphthalein, sulfisoxazole diethanolamine, and radioiodine (I^{131}) (911). The amount of sulfonamide excretion from kidneys was found to be dependent on the degree of protein binding (912). Protein binding was also investigated in relation to the antibacterial activity of long-acting sulfonamides (913). Using an equilibrium dialysis method, Nakagaki, *et al.*, evaluated binding between bovine serum albumin and five kinds of sulfanilamides (914). At low sulfonamide concentrations, Scholtan demonstrated that the protein-binding ratio follows Freundlich's rather than Langmuir's adsorption isotherm (915).

Wood reviewed the absorption, distribution, excretion, uses, and toxicity of salicylates (916). The influence of 2-methyl-2-propyl-1,3-propanediol bis(isopropylcarbamate) on the absorption of salicylates and acetylsalicylic acid was discussed in another paper (917). Levy and Gagliardi investigated the gastrointestinal absorption of aspirin anhydride (918). Accumulation of certain drug anions in gastric mucosal cells following oral administration was reported (919). Efficacy and toxicity were evaluated in a comparative blood level study of choline salicylate and acetylsalicylic acid (920). *In vitro* and *in vivo* properties of a new aluminum derivative of acetylsalicylic acid were also investigated (921).

Some factors affecting the absorption of vitamins were discussed by Campbell and Morrison (922). The influence of intrinsic factor on the uptake of vitamin B_{12} by the small intestine of the Rhesus monkey has been explored—maximum absorption occurred in the lower ileum (923). Absorption, deposition, excretion, and duration of action of hydroxycobalamin were investigated, with emphasis on the treatment of vitamin B_{12} deficiencies and pernicious anemia (924). Studies were conducted on the tissue distribution and storage forms of vitamin B_{12} in dogs after injection or oral administration (925). Another worker discussed the effect of deficiencies of certain B vitamins and ascorbic acid on the absorption of vitamin B_{12} (926). It was reported that glutamic acid does not increase the absorption of vitamin B_{12} (927). In dogs, absorption of vitamin B_{12} in the presence of intrinsic factor occurs primarily in the ileum (928). Waife, *et al.*, reported on the treatment of pernicious anemia patients using oral vitamin B_{12} in the absence of intrinsic factor; evidence of absorption was measured by urinary excretion methods (929). Miller, *et al.*, discussed the possible absorption of intrinsic factor into the plasma of rats (930). The intestinal absorption of L-ascorbic acid-1-C^{14} was studied *in vitro* and *in vivo* in rats and hamsters (931).

PHARMACOGNOSY[1]

Two general reviews of pharmacognosy have been published: Evans surveyed the advances in pharmacognosy and stressed the need for more fundamental research on specific plants (932); Farnsworth also reviewed the current status of botanical drugs and discussed thin-layer chromatography as a basic research tool in pharmacognosy (933). Extensive listings of medicinal plants of Casamance (Senegal) (934) and the Soviet Union (935) were presented. In another

[1] The writers thank Dr. G. H. Svoboda for his suggestions concerning the preparation of this section.

TABLE I.—PHARMACOGNOSTIC INVESTIGATIONS

Plant	Ref.
A	
Acacia seyal	(939)
Acer palmatum	(940)
Acervus species	(941)
Achillea species	(942–945)
Acokanthera oblongifolia	(946)
Adonis vernalis	(947)
Alangium lamarckii	(948)
Albizia gummifera	(949)
Aloe species	(950)
Amaryllis hybrida	(951)
Amaryllis parkeri	(952)
Ammi visnaga	(953, 954)
Anemarrhena asphodeloides	(955, 956)
Anemone nigricans	(957)
Andropogon schienanthus	(958)
Anemopsis californica	(959)
Angelica species	(960–963)
Anthemis nobilis (*Matricaria chamomilla*)	(964, 965)
Apium graveolens	(961)
Aquilegia species	(966)
Aralia elata	(967)
Arbutus menziesii	(968)
Argemone mexicana	(969)
Arnica foliosa	(970)
Arnica montana	(970, 971)
Artemisia species	(972–974)
Ascosparassis species	(941)
Aspergillus fumigatus	(975)
Aspidosperma album	(976, 977)
Atropa belladonna	(978)
B	
Banisteria lignum	(979)
Berberis barandana	(980)
Berberis vulgaris	(981)
Betonica officinalis	(982)
Bladhia japonica	(983)
Boswellia serrata	(984)
Buxus alkaloids	(985, 986)
C	
Caccinia glauca	(987)
Caesalpinia bonducella	(988)
Callitrus drummondii	(989)
Calpurnia subdecandra	(990)
Campanula rotundifolia	(991)
Cannabis indica	(992)
Capsicum annum	(993)
Carissa carandas	(994)
Carissa spinarum	(994)
Carya pecan	(995)
Casimora species	(996)
Cassia (Senna)	(997)
Catalpa ovata	(998)
Catha edulis	(999)
Catharanthus lanceus (*Vinca lancea*)	(1000)
Cephalotaxus drupacea	(1001)
Cephalotaxus fortunei	(1001)
Chaetomorpha capillaris	(1002)
Cheiranthus allionii	(1003)
Cinchona alkaloids	(1004)
Cirsium martimum	(1005)
Cissampelos pareira	(1006)
Citrullus colocynthis	(1007)
Cladophora rupestris	(1002)
Clematis terniflora	(1008)
Cnidium officinale	(961)
Codium fragile	(1002)
Convallaria majalis	(1009, 1010)
Corchorus olitorius	(1011)
Cordyceps capitata	(1012)
Coronilla varia	(1013)
Corydalis ambigua	(1014)
Crotalaria species	(1015–1017)
Croton species	(1018, 1019)
Cyathea fauriei	(1020)
Cyclea peltata	(1006)
Cynanchum caudatum	(1021)
Cyperus rotundus	(1022)
Cytisus praecox	(1023)
D	
Dalbergia latifolia	(1024)
Daphne mezereum	(1025)
Datura species	(1026–1030)
Delphinium dictyocarpum	(1031)
Dentaria pinnata	(1032)
Dichroa febrifuga	(1033)
Digitalis species	(1034–1038)
Dioscorea species	(1039–1043)
Diplopterygium glaucum	(1044)
Discomycetes	(1045)
Dryopterus crassirhizoma	(1046)
Duboisia myoporoides	(1047)
E	
Ephedra sinica	(1048)
Ergot alkaloids	(1049)
Ericaceae alkaloids	(1050)
Ervatamia dichotoma	(1051)
Erysimum canescens	(1052)
Erythrophleum ivorense	(1053)
Eucalyptus species	(1054, 1055)
Eugenia maire	(1056)
Eupatorium maculatum	(1057)
F	
Fagara xanthoxyloides	(1058)
Ficus septica	(1059)
Flammulina velutipes	(1060)
Fraxinus rhynchophylla	(1061)
Fumaria parviflora	(1062)
G	
Galerina species	(1063)
Genista aetnensis	(1064)
Genista raetam (*Retama raetam*)	(1065)
Geranium palustre	(1066)
Ginseng	(1067–1071)
Gleditschia horrida	(1072)
Glycosmis arborea	(1073)
H	
Helenium aromaticum	(1074)
Helicostylum species	(1075)
Helleborus species	(1076–1078)
Hibiscus trionum	(1079)
Hunteria eburnea	(1080–1082)
Inula helenium	(1083)
Iris kamaonensis	(1084)
Isodon trichocarpus	(1085)
Isotoma longiflora	(1086)
J	
Jasione montana	(991)
Juniperus species	(1087–1089)
K	
Kaempferia rotunda	(1090)
Kopsia species	(1091)
L	
Lampteromyces japonicus	(1092)
Laurus nobilis	(1093)

Plant	Ref.
Lavandula species	(1094, 1095)
Leptospermum seoparium	(1056)
Leucothoe grayana	(1096)
Levisticum officinale	(961)
Ligularia tussilaginea	(1097)
Ligusticum acutiloba	(961)
Linum usitatissimum	(1030)
Lobelia urens	(1098)
Lupinus species	(1099)
Lycium chinense	(1100)
Lycopodium species	(1101–1103)
M N	
Machilus species	(1104–1106)
Magnolia kachirachirai	(1107)
Majorana hortensis	(1108)
Menispermaceae	(1109, 1110)
Mentha piperita	(1111)
Metanarthecium luteo-viride	(1112)
Michelia champaca	(1113)
Mitragyna species	(1114–1117)
Myrtus communis	(1054)
Narcissus alkaloids	(1118–1120)
P	
Paeonia albiflora	(1121)
Pancratium maritimum	(1122)
Paulownia tomentosa	(1123)
Pergularia extensa	(1124)
Peschiera affinis	(1125)
Physostigma venenosum	(1126)
Phyteuma spicatum	(991)
Pieris japonica	(1127)
Pimpinella heyneana	(1128)
Pinus species	(1129, 1130)
Piper methysticum	(1131)
Pithecolobium dulce	(1132)
Plantago major	(1133)
Platycodon grandiflorum	(991)
Podophyllum peltatum	(1134)
Polygonum aviculare	(1135)
Pongamia glabra	(1136)
Populus grandidentata	(1137)
Prangos pabularia	(1138)
Pulsatilla grandis	(1139)
R	
Rauwolfia species	(1140–1144)
Rhamnus Purshiana	(1145)
Rhazya stricta	(1146–1148)
Rheum palmatum	(1149)
Ricinocarpus stylosus	(1150, 1151)
Rosmarinus officinalis	(1152)
Rumex species	(1153–1155)
Ruta graveolens	(1156)
S	
Salix species	(1157–1159)
Salvia species	(1160)
Sarcostemma viminale	(1161)
Sargassum natans	(1162)
Scabiosa succisa	(1163)
Schoenocaulen officinale	(1164, 1165)
Sciadopitys verticillata	(1166)
Scilla maritima	(1167)
Securinega suffruticosa	(1168, 1169)
Securinega virosa	(1170)
Simaba cedron	(1171)
Sinocalamus oldhamii	(1172)
Sinomenium acutum	(1173)
Skytanthus acutus	(1174)
Smilax sieboldi	(1175)
Solanum species	(1041, 1176–1178)
Sophora species	(1179, 1180)
Sphenomeris chusana	(1020)
Stephania japonica	(1181)
Strychnos species	(1182)
Sweetia panamensis	(1183)
Symphytum species	(1184)
T	
Tabernaemontana pachysiphon	(1185)
Tacca leontopetaloides	(1186)
Tagetes species	(1187)
Tecoma stans	(1188)
Thalictrum dasycarpum	(1006, 1189)
Thymus vulgaris	(1190)
Tilia species	(1191, 1192)
Tripetaleia paniculata	(1193)
Tripterygium wilfordii	(1194)
U V	
Ulva lactuca	(1002)
Ungernia species	(1195, 1196)
Valeriana angustifolia	(1197)
Veratrum album	(1198)
Vinca minor	(1199–1201)
Vinca rosea (*Catharanthus roseus*)	(1202–1205)
Virgilia oroboides	(1206, 1207)
Vitex agnus-castus	(1208)
W X Y	
Waltheria americana	(1210)
Wistaria floribunda	(1211)
Withania species	(1212–1216)
Xanthorhiza simplicissima	(1209)
Yucca aloefolia	(1217)
Yucca guatamalensis	(1218)

paper, the development of storage and retrieval techniques for punched cards on phytochemical data was reported (936). Thirty tannin-containing drugs were classified according to their ultraviolet absorption spectra (937). A procedure utilizing fresh plant material has been described for alkaloid screening of plants in the field (938).

Pharmacognostic Investigations.—This section of the review is primarily concerned with those references pertaining to isolation and identification of plant constituents. Table I lists alphabetically each plant studied, followed by the appropriate references to the bibliography.

Methodology.—Germination, growth, and alkaloid synthesis of *Datura stramonium* after various treatments have been investigated (1219, 1220). Research on biosynthetic pathways to coumarin formation in plants was published by Brown (1221). An extensive investigation was conducted concerning the influence of environmental factors on the growth and oil production of some species of Labiatae (1222–1224). Growth characteristics of spearmint tissue were explored with a dual-carboy culture apparatus (1225). Alkaloid production by *Claviceps paspali* was studied in submerged culture (1226), while laboratory culture experiments with *C. purpurea* were

reported in two different articles (1227, 1228). Teuscher discussed the influence of amino acids on the biosynthesis of clavine alkaloids in saprophytic culture (1229). Suspension cultures of *Digitalis lanata* and *D. purpurea* were employed by Staba and Lamba in the experimental production of cardiac glycosides (1230). Microbiological hydroxylation of digitoxigenin derivatives by *Absidia orchidis* was recorded (1231).

Hoerhammer, *et al.*, used thin-layer chromatography for identification and differentiation of *Strophanthus* glycosides (1232), while other investigators quantitatively determined the principal alkaloids of opium using this technique (1233). A new two-dimensional thin-layer chromatography technique was used in phytochemical studies of the alkaloids of *Pancratium maritimum* (1234). Ion-exchange, paper and thin-layer chromatography in pharmacognostic instruction have been discussed by Reuter (1235). Another paper revealed thin-layer chromatography to be useful in detecting adulteration of *Tussilago farfara* with *Petasites* leaves (1236). Thin-layer chromatography was also employed for the separation and estimation of some plant polyhydroxy anthraquinones (1237). Schwarz effected a chromatographic separation of steroid compounds on a magnesium silicate layer without binding agents (1238).

More efficient extraction of plants was accomplished through the application of certain mathematical principles to maceration and percolation (1239). Stanev and Elenkov studied the dynamics of morphine extraction from poppies (1240). A laboratory method was developed for obtaining extracts of *Leonurus cardiaca* (1241). Other investigators evaluated effects of various factors on extraction of active ingredients from medicinal plants (1242). Various aqueous-alcoholic mixtures were employed under a variety of conditions to study the efficiency of extraction of *Digitalis purpurea* leaves (1243). Deacylation and copper complexing were used to fractionate two major water-soluble polysaccharides from *Pinus sylvestris* (1244). Decomposition of rutoside was reported when ether saturated with water was used for its extraction from rue (1245). The effect of dispersion on the extraction of active substances from medicinal plants (1246) and the extraction of belladonna herb with the aid of surfactants (1247) were investigated. Surfactants were also used in preparing fluid extracts of thyme (1248).

Tyler and Stuntz reported a qualitative test for alkaloids in studies of higher fungi (1249). A hemolytic index was described for evaluation of saponin extracted from the roots of *Gypsophila paniculata* (1250). Standardized conditions for production of good quality agar from seaweed were suggested (1251). Spray drying for the isolation of various alkaloids and glycosides has been discussed (1252). Ultrasound was employed successfully in the extraction of plants containing alkaloids (1253). It was also reported that the use of ultrasonic energy to isolate alkaloids shortens maceration and extraction times and increases the yield (1254).

CONCLUSION

The number and variety of publications in pharmaceutical science continue to demonstrate the complexities of this field of study. It was the aim of this review to facilitate presentation of some of these advances to those engaged in pharmaceutical research.

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[2] *Index Medicus* abbreviations were used for journals not listed in *Chemical Abstracts*. In a few instances where the writers were unable to obtain late 1963 issues, references were obtained from *Current Contents*.

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Research Articles

Method for Evaluating Behavioral Effects of Central Depressants

By MARVIN COHEN* and JOHN W. NELSON

A new method for the evaluation of central nervous system depression is presented. It is based on the scoring of behavioral responses to subhypnotic doses of central depressants. The application of the method to the study of two different types of depressants, pentobarbital and chlorpromazine, both alone and in combination, is shown. The time-response scoring method appears to be useful as a screening method and as a tool for more theoretical studies when appropriate modifications are made for different types of pharmacological agents.

The problem of drug interaction and its evaluation is a fundamental one in the field of general pharmacology. Studies in this area, such as those of Bliss (1), Gaddum (2), Berger and Lynes (3), and Gruber (4) have led to an accumulation of considerable information. Such data, however, have largely been obtained by means of toxicity studies (1) or by the measurement of sleeping times in cases where central depressants have been employed (2–4). Gruber (4) has commented on studies of this type by stating that the data obtained in this way, being only relative values, cannot be measured and compared with any degree of accuracy. More quantitative studies, using animals given subhypnotic doses of depressants, have been performed by such workers as Swinyard (5), Lim

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