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Review Article

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A Literature Review

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CONTENTS

[Contents for Part I of this review appeared in the July issue, THIS JOURNAL, 52, 613(1963).]

RADIOISOTOPES

BOUSQUET has reviewed radioisotope applications to cosmetic analysis and product evaluation (536). Methods and apparatus were described for the investigation of aqueous properties and structure of disperse bodies with the aid of radioactive isotopes (537). Appino, *et al.*, presented a radioisotopic method for the evaluation of emulsions which was applicable to either water-in-oil or oil-in-water systems (538). Radioactive tracer techniques were used by Banker to study uniformity of distribution of phosphorus compounds in tablet matrices (539). Scintillation counting was employed for studying adsorption and hydrogenation of radioactive crotonic and vinylacetic acids on thiophene-poisoned palladium (540). Continuous measurement of diffusion coefficients of gases in liquids using glass scintillators made it possible to monitor slow diffusion processes for several hundred hours without disturbing the system by sampling (541). Labeled atoms were also used in the determination of diffusion coefficients of drugs in polymers (542). Radioactive isotopes were used in studying vitamin B_{12} absorption (543), and Ruggiero

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and Skauen have described a chick embryo technique for evaluation of radioactive sodium iodide absorption from various ointment bases (544, 545).

A few papers dealt with the use of radioactive isotopes in pharmaceutical sterilization methods. Sterilization by means of ionizing radiation was reported to be advantageous only for preparations containing compounds such as proteins, enzymes, and steroids which cannot be sterilized by conventional techniques (546). Radiation sterilization of antibiotics (547) and sterilization of ampuled drugs and drug solutions (548) have also been investigated. Schwenker and Vogt discussed the effects of sterilization doses of ionizing radiation on liquid and solid petrolatum (549).

Rames and Bailey studied the chemical effect of high level gamma irradiation on blood glucose *in vitro* (550). A review of the preparation and production control of iodine-131 and colloidal gold-198 was published (551). Two methods for the preparation of tritium-labeled oxytocin were reported (552), and Peng described a method for the preparation of soluble radiophosphate (553). The effects of ionizing radiation on two gelatin fractions were studied (554). When vitamin B_1 hydrochloride crystals were irradiated with Co^{60} γ-rays, a more dense, less hygroscopic material was obtained (555). Radiochemical purity of tritium exchange-labeled barbital was the subject of another paper (556). A review article discussed the application of radioisotopic indicators to paper chromatography (557). Stability of labeled sodium polymetaphosphate was investigated by means of a chromatographic method (558). In studying the mechanism of action of phenolic disinfectants, Judis investigated the release of radioactivity from C^{14}-labeled *Escherichia coli* (559).

Christian, *et al.*, described a 2π liquid scintillation counter for determining the radioactivity of large samples, including man and animals (560). The assembly and operating characteristics of a 4π liquid scintillation detector were reported by Dunavant (561). A Co^{60} γ-irradiator with an unusually high radiation intensity per curie of cobalt has been developed for use in chemical research (562). Rhodes disclosed a simple formula for mass absorption coefficients near the K absorption edge (563), and Evans proposed a simplified self-absorption correction for isotopes emitting weak β-particles (564). Parameters affecting the resolution of a proportional counter have been discussed (565). In another publication, Meade and Stiglitz considered improved solvent systems for liquid scintillation counting of body fluids and tissues (566).

BIOPHARMACEUTICS

Biopharmaceutics is that area of pharmaceutical science primarily concerned with effects of pharmaceutical formulation on the biological activity of medicinal agents. Research in this area requires a certain amount of knowledge in allied fields such as biochemistry, pharmacology, and physiology, to name just a few. Several references in these related areas have been included as part of the review.

Friend discussed the importance of pharmaceutical formulation on the clinical efficacy of drugs and suggested some factors to be considered in the development of pharmaceuticals (567). Problems encountered in the design and presentation of medicinal substances were reviewed (568). Three papers discussed evaluation of new drugs (569), clinical trials of drugs (570), and drug screening and evaluation procedures (571). Pfeiffer described some problems encountered in exploratory trials of new drugs in man and ways of overcoming them (572). The use and abuse of mixtures of active drugs were reviewed (573), while another paper discussed unexpected hazards associated with drugs and chemicals (574).

Automation in biopharmaceutics and related areas was treated by several writers. Applications of data-processing equipment in clinical drug evaluation were reviewed (575). Machine retrieval of pharmacodynamic data was reported by Dietrich (576). An automatic digital computer was employed for the solution of some chemotherapeutic problems (577). Also published was a paper on the use of program-controlled automatic calculators for dosage computations (578).

Bousquet, in a review on the pharmacology and biochemistry of drug metabolism, discussed some of the biochemical reactions undergone by drugs (579). Another writer considered the relation of pharmacology to medicine and pharmacy (580), and contributions to medicine by research in pharmacology were summarized by Riker (581). In a symposium on clinical drug evaluation, Brodie described some of the difficulties in extrapolating data on metabolism of drugs from animal to man; he pointed out that the greatest difficulty is species difference in biotransformation of drugs (582). Several references were cited in a review of methods for studying the anti-inflammatory steroids (583). Kirsner, *et al.*, discussed some problems in the evaluation

of gastrointestinal drugs and ways of overcoming them (584). The effect of intestinal motility on the absorption of sodium in man was investigated (585). Regulation of gastric emptying after meals containing citric acid and salts of citric acid was studied by Hunt and Knox (586).

A theoretical and experimental approach to various facets of drug-receptor interaction has been published (587). In their studies on drug receptors in smooth muscle, Takagi and Iwaki (588) and Iwaki (589, 590) investigated the action of reversible and irreversible antagonists on vascular smooth muscles. A gel filtration method was described for the study of drug-protein binding; quantitative separation of bound and unbound drug was obtained from Sephadex columns (591). Barlow, *et al.*, also measured drug-plasma binding with the aid of Sephadex (592). Semipermeable membranes and electrophoresis were used to study the interaction of sulfapyroxyline and sulfamerazine with serum protein (593). The binding of nitrofurans by proteins was also investigated (594). Scholtan examined the binding of long-acting sulfonamides on human serum proteins with a new small-capacity dialyzator (595), while Scholtan and Schmid showed that the binding of penicillin to serum and tissue proteins was directly related to penicillin concentration but inversely related to temperature (596). Dialysis experiments and radioactive histamine were used in studying histamine binding by heparin (597). Another report described the interactions of xanthine molecules with bovine serum albumin (598).

Effects of Formulation.—Two methods have been described for determining whether patients are actually taking their medication: Swintosky used riboflavin as a marker which could be detected in urine (599), and Ryan, *et al.*, proposed a similar procedure using phenolsulfonphthalein (600). If phenolsulfonphthalein is present, the urine will turn violet when made basic. Aerosol administration of ergotamine tartrate for the treatment of migraine headache was investigated in a study which compared aerosol administration with parenteral injection, oral and sublingual dosage, and rectal suppositories (601). Atropine micro-aerosols and their effects on airway resistance in man were studied (602). In another study a new noscapine formulation for relief of symptoms associated with respiratory tract disorders was also described (603). Schnell and Husa studied the permeability of red corpuscles to water-soluble organic iodine compounds (604), while Shaw and Husa observed the hemolysis of red corpuscles by various substances in the presence of sodium chloride (605). Experimental work on the cause of pain following injection of parenteral pharmaceuticals was published (606, 607). Thoma, *et al.*, examined the effect of bentonite and Veegum on the activity of a series of antiseptics (608). Two papers were published on the subject of physiological availability: one discussed the influence of granulating agents on biological availability of tablet medication (609); the other dealt with the relationship between disintegration time and physiological availability of medication in long-acting tablet formulations (610). Antibacterial activity of mixtures of quaternary ammonium compounds and hexachlorophene was investigated (611).

An *in vitro* method which complies with biological behavior was described for the evaluation of antacids (612), and Newey reported that peptone should be included in artificial gastric juices for antacid testing (613). Clinical and experimental observations on a new antacid were also published (614). Beekman discussed the preparation and properties of some new antacids containing aluminum and magnesium (615, 616). In a study of the influence of common antacids on intragastric pH, dihydroxy aluminum sodium carbonate was found to have a more significant prolonged effect than other compounds investigated (617). Continuous recording of pH by a glass electrode *in situ* was used in assessing the results of diet, antacids, and anticholinergic agents on gastric and duodenal acidity (618). Davison, *et al.*, studied the effects of buffered and unbuffered acetylsalicylic acid on the gastric acidity of normal humans; compared with a control, neither aspirin nor buffered aspirin produced appreciable changes (619). Toxicity of aspirin preparations to the gastrointestinal tract was the topic of another paper (620).

Effects of Physicochemical Properties.—Nelson has discussed physicochemical and pharmaceutic properties of drugs that influence the results of clinical trials (621). The role of ionization constants in the absorption of drugs from the gastrointestinal tract was reviewed (622). An absorption-rate hypothesis, based on physicochemical properties, for the absorption of drugs after subcutaneous implantation was presented by Ballard and Nelson (623). Aqueous/lipid partition coefficient was found to be an important factor in percutaneous absorption of weak electrolytes (624). Treadwell, *et al.*, investigated conditions controlling sterol absorption (625). Hofmann and Borgström suggested that lipids are probably absorbed from the in-

testinal tract as micelles with bile salts acting as transport carriers (626).

Physicochemical factors influencing the absorption of erythromycin and its esters were investigated by Nelson; dissolution rates of erythromycin and some of its esters in fluids simulating gastric and intestinal juices were presented (627). A biological study of some new derivatives of demethylchlortetracycline has been published (628). A report on factors influencing the absorption of griseofulvin from the gastrointestinal tract has also been published (629). Physiological availability of riboflavin and thiamine from "chewable" vitamin products was determined by Morrison and Campbell (630). Of the nine products they studied, six showed incomplete riboflavin availability as measured by urinary excretion. A chromatographic method for testing the availability of ionic iron from iron chelates was published (631). In another article, the use of an iron-sorbitol-citric acid complex in iron-deficiency anemia was disclosed (632). Dettbarn suggested that the cationic form of local anesthetics is intrinsically the most potent (633). A series of papers was published on the relations between physicochemical properties and the action of local anesthetics (634–637). Truitt and Morgan compared gastrointestinal absorption rates of plain and buffered acetylsalicylic acid (638). The potentiation of injectibles through Al_2O_3 adsorption has been studied (639, 640).

Effect of Particle Size.—The influence of particle size on systemic effects after breathing potent medicated aerosols was investigated (641). Three papers relating griseofulvin absorption to particle size were published: Kraml, *et al.*, studied the effect of particle size and addition of surfactants and corn oil on the serum levels of griseofulvin in rats (642). In another paper, Kraml, *et al.*, found that micronized griseofulvin was absorbed better from the gastrointestinal tract than nonmicronized material (643). The third paper, by Atkinson, *et al.*, discussed the relation of griseofulvin particle size to human blood levels (644). They found that 2.7 μ diam. griseofulvin was twice as effectively absorbed as particles measuring 10 μ in diameter. Rabbit blood levels were compared after administration of metal salts and various particle sizes of chloramphenicol (645). In another study, the effects of particle size and dissolution rate on blood concentration following oral administration of N′-(5-ethyl-1,3,4-thiadiazol-2-yl) sulfanilamide were reported; an instrument for measuring dissolution rate was also described (646). The influence of particle size and solubilizers on the absorption of spironolactone from the gastrointestinal tract was studied (647). Purity was found to be more important than particle size to the anthelmintic efficacy of phenothiazine (648).

Absorption Control.—Several reviews were published on various aspects of prolonged-action medication (649–652). An article on the dangers of using oral sustained-release medication was also published (653). Horstman used a double-blind study to show that an extended-action tablet was more effective than a regular tablet of a given drug (654). Two-layer tablets with prolonged action were investigated (655). Exponential release of cyclobarbital calcium from different oral sustained-action dosage forms in artificial gastric juices was reported (656).

Moeller and Rider evaluated a long-acting anticholinergic-antacid preparation in the treatment of peptic ulcer and other diseases of the digestive tract (657), while Hock described clinical evaluation of an anticholinergic agent in a sustained-release dosage form (658). The relationship between dissolution of sustained-release granules and rabbit blood levels of chloramphenicol was investigated (659). Clinical observations of several diabetic patients taking phenethylbiguanide timed-disintegrating capsules were reviewed (660). Weller, *et al.*, also studied the use of phenethylbiguanide timed-disintegrating capsules in the management of diabetic patients (661). The effect of sustained-release acetazolamide on intraocular pressure in man was investigated (662). Rudolph, *et al.*, discussed the use of multiple miniature long-acting antihistamine tablets in allergy (663), and the clinical and physiological effectiveness of timed-release coronary dilator therapy was investigated by Robbins and Thompson (664). Two reports dealt with the release of iron from oral sustained-action dosage forms (665, 666).

The rate of absorption and duration of plasma level after administration of different pharmaceutical preparations of meprobamate were investigated (667). Hollister compared blood levels from compressed tablets and two delayed-action capsule forms of meprobamate (668). In another study, Hollister evaluated two phenothiazine tranquilizers administered in coated tablet and prolonged-action dosage forms (669). S^{35}-labeled trimeprazine tartrate was used to study the effect of sustained release on absorption and excretion (670). Cass and Frederik discussed clinical evaluation of long-release and capsule forms of pentobarbital sodium (671). Enteric-

coated tablets of prednisolone (672) and an oral sustained-release form of methylprednisolone have been investigated (673). A vitamin B_{12} preparation with retarded absorption was reported by Schwartz, *et al.* (674), and Arnold, *et al.*, found that an oil-aluminum monostearate depot preparation of vitamin B_{12} prolonged levels up to 27 days (675).

A study of iron dosage and absorption demonstrated the existence of a linear relationship between dose and absorption when both are plotted on logarithmic scales (676). Blood and urine levels after oral doses of a new soluble tetracycline have been investigated (677). Atkinson, *et al.*, analyzed human blood levels produced by different dosage schedules of griseofulvin; rate of absorption and blood level appeared to be linearly related to the logarithm of the dose (678). Different dose schedules of amethopterin and the resultant serum and tissue concentrations and urinary excretion patterns were examined (679). The stimulating effects of some inhibitors of drug metabolism on excretion of ascorbic acid and drug metabolism were also studied (680).

Kinetic Studies.—Applications of chemical kinetics to the absorption and excretion of chemicals have been reviewed (681). Taylor and Wiegand have demonstrated the usefulness of an analog computer in analyzing models of biological processes involving plasma-drug kinetics (682). To illustrate, they examined drug-plasma kinetics after sustained-release medication. The use of digital computers for fitting kinetic data to models was reported by Berman, *et al.* (683). Berman, *et al.*, also described some formal approaches to the analysis of kinetic data in terms of linear compartmental systems (684). Another researcher described a method for the determination of absorption rates by integration of rates of appearance and disappearance in blood (685).

An *in vitro* study of the kinetics of penetration of sulfonamides through the intestinal barrier was published (686). Nelson, *et al.*, have studied the influence of tolbutamide absorption rate on the rate of decline of blood sugar levels in normal humans (687), and Nelson discussed the zero-order oxidation of tolbutamide *in vivo* (688). In another paper, Nelson examined the kinetics of excretion of sulfonamides during therapeutic dosage regimens (689). A kinetic investigation of blood sugar lowering by various types of insulin preparations resulted in a method for the determination of rate constants (690).

Schwarz, *et al.*, studied the resorption and biological half-life of glycerin in humans (691). The relationship between plasma salicylate concentration and rate of urinary salicylate excretion was explored (692). Also investigated was the effect of protein binding on the renal excretion rate of salicylic acid derivatives; constants for excretion velocity and half-life were reported (693). Penetration kinetics of basic drugs such as aminopyrine through the intestinal barrier *in vitro* were discussed (694). Garrett, *et al.*, used an analog computer to study the influence of steroids on Ca^{47} dynamics in dogs (695). Kinetic studies were also used for investigating fungicidal action (696) and the activity of pilocarpine and eserine (697). Distribution and excretion kinetics of a new dextran were reported (698). This new dextran was made by direct microbiological conversion of sucrose into a material of appropriate molecular weight. Moll and Code investigated the rates of absorption of sodium and potassium from the stomach and upper small bowel of rats (699, 700). The kinetics of accumulation of radioiodine by the thyroid over both short- and long-time intervals was also investigated (701, 702).

Absorption Mechanisms.—Mechanisms of drug absorption and excretion have been reviewed (703). Hindle and Code reported some differences between duodenal and ileal absorption; the duodenal process appeared directed toward establishment of an equilibrium with blood, while the ileal process tended more toward absorption (704). The relationship between pharmacological antagonsim and membrane potential has been investigated (705). Rectal absorption of antibiotics was also studied (706). Ballard and Nelson reviewed absorption of implanted solid drug (707), and Barr cited over 200 references in a review of percutaneous absorption (708). Barriers to skin penetration were reported in another paper (709). The influence of urinary pH on the excretion and biotransformation of salicylic acid derivatives was investigated (710). Kostenbauder, *et al.*, described methods for controlling urinary pH and the resultant effect on sulfaethidole excretion in humans (711). Other investigators discussed the adjustment of urine pH in chemotherapy of urinary-tract infections (712).

An active transport system for absorption of folic acid from the small intestine of the rat has been reported (713). Amino acid absorption in the rat upper small intestine was found to be an active process dependent, at least in part, on vitamin B_6 (714). Considerable research effort was devoted to mechanisms involved in vitamin B_{12} absorption (715–718). Measurements of

folic acid and D-xylose absorption have been used as tests of small-intestine function (719). Beck, *et al.*, described the use of D-xylose blood level time curves as an index of intestinal absorption (720). In their studies on the mechanism of intestinal absorption of sugars, Bihler and Crane (721), and Bihler, *et al.* (722), investigated the influence of cations on the active transport of sugars. Renal disposal of salicyluric acid has been discussed (723). Schanker and Jeffrey (724) and Schanker and Tocco (725) have reported their work on the pyrimidine transport process of the small intestine. The influence of bioelectric potentials on absorption and distribution of organic electrolytes was investigated (726). Barry, *et al.*, concluded that potential differences arising from ion movements across the gut were not responsible for water transport (727).

Drug Absorption: Antibiotics.—Physical, chemical, and pharmacodynamic studies of viomycin have been reviewed (728). Griffith and Black presented a comparison of blood levels after oral administration of erythromycin and erythromycin estolate (729). They reported that a 1000-mg. oral dose of erythromycin is needed to obtain the same blood levels produced by a 250-mg. oral dose of erythromycin estolate. Serum levels following parenteral administration of paromomycin (730) and modes of excretion and accumulation of water-soluble and basic antibiotics in the mouse (731) have been investigated.

Serum binding, distribution, and excretion of tetracycline and a new analog, methacycline, were compared in humans (732). Scheiner and Altemeier studied the factors inhibiting absorption and effective therapeutic levels of demethylchlortetracycline hydrochloride and found that milk, milk products, and aluminum hydroxide gel inhibited absorption (733). When combined with lysine, tetracycline and chlortetracycline were absorbed into the rat intestine *in vitro* at a faster rate than either antibiotic alone (734). Antibacterial activity, *in vitro* absorption, diffusion, and elimination of tetracycline-L-methylenelysine by man have been investigated (735). Krondl, *et al.*, studied the influence of chlortetracycline and neomycin on fat digestion and absorption in rats (736).

The absorption of some new chloramphenicol esters has been reported (737). In their studies on the absorption and excretion of drugs, Kakemi, *et al.*, measured chloramphenicol blood levels after administration of the free drug or its esters (738). In another paper, they discussed determination of chloramphenicol in urine and its metabolic rate (739). They also studied absorption of chloramphenicol and the effect of metal salts on chloramphenicol absorption from the rat stomach and small intestine (740).

Russell reviewed some of the properties and pharmacological actions of new synthetic penicillins (741). Bacteriological and clinical pharmacological investigations of methicillin and oxacillin have been reported; methicillin was found unstable in acid solution but oxacillin was well absorbed orally from an empty stomach (742). The effect of ascorbic acid on the absorption of potassium phenoxymethylpenicillin was examined (743). Cheng and White studied the effect of orally administered neomycin on the absorption of penicillin V and discovered that neomycin inhibited absorption (744). Chemotherapeutic properties of some α-substituted benzylpenicillins have been described (745). Administration of penicillin decreased the coefficient of intestinal absorption of *p*-aminohippuric acid in man and rat (746).

Drug Absorption: Organic.—Richmond and Girdwood (747) and Christensen (748) have published papers dealing with amino acid absorption. Everted hamster intestinal sacs were used to study amino group requirement for transintestinal transport of amino acids against a concentration gradient (749). Absorption, distribution, and excretion of ϵ-aminocaproic acid following oral or intravenous administration to man were investigated (750). Absorption of amino acid mixtures from the small intestine of the rat was also investigated (751). Equimolar mixtures and mixtures simulating the amino acid composition of egg albumin, casein, and zein were studied. Gastrointestinal absorption and renal excretion of hydroxyproline peptides in humans (752) and glucose, amino acid, and urea absorption from the canine intestine (753) were explored.

Levy and Sahli compared the gastrointestinal absorption of aluminum acetylsalicylate and acetylsalicylic acid (754) and Leonards demonstrated the presence of acetylsalicylic acid in plasma following oral ingestion of aspirin (755). Water and electrolyte pharmacodynamics of aspirin absorption were investigated (756). Tanaka, *et al.*, studied the effect of glucosamine on absorption and excretion of salicylic acid derivatives in rabbits and dogs (757, 758). Absorption of salicylic acid derivatives from the rat stomach and small intestine was investigated by Kakemi, *et al.* (759, 760). In another paper, Kakemi, *et al.*, described a method for the sepa-

ratory determination of human urinary metabolites of *p*-aminosalicylic acid (761). The influence of a nonionic surfactant on percutaneous penetration of diethylamine salicylate was studied (762), and coefficients of intestinal absorption of *p*-aminohippuric acid in man and some laboratory animals were reported (763).

Studies on the digestion, absorption, and metabolism of castor oil were published (764). Absorption, metabolism, and excretion of some edible dyes have been investigated (765, 766). Urinary excretion of tritiated butylated hydroxyanisole and butylated hydroxytoluene in the rat was studied by Golder, *et al.* (767). The absorption of bretylium and related quaternary ammonium salts from the alimentary tract has been investigated (768). Kaul studied the urinary excretion of tetrahydroaminoacridine (769), and Weiner and Lack found that little, if any, absorption of bile salts took place in the proximal portion of the guinea pig intestine (770).

Results of studies on absorption by the guinea pig intestine of cyanocobalamin incubated with intrinsic factor were published (771). Rat utilization of riboflavin and thiamine given orally or parenterally at periodic intervals was investigated (772). Booth and Brian studied the absorption of tritium-labeled pyridoxine hydrochloride in the rat (773). They found pyridoxine to be rapidly absorbed from the upper intestinal tract regardless of the amount administered. Percutaneous absorption of nicotinic acid and ethyl nicotinate through human skin was also investigated (774).

In their studies on the absorption and excretion of medicaments, Kakemi, *et al.*, used ion-exchange resins to separate metabolic products of isoniazide from the urine (775). The absorption of a bronchodilator, isoetharine (776), and absorption and excretion of sulfamethomidine, a "long-acting" sulfonamide (777), have been investigated. Oral absorption of sulfadimethylpyrimidine was studied (778). Gantt, *et al.*, discussed the gastrointestinal absorption of spironolactone (779). Studies on the distribution and excretion of mebrophenhydramine in rats have been reported (780). Absorption, excretion, and fate of prodilidine were studied in the rat by perfusing the small intestine and measuring drug concentration in the effluent (781).

Drug Absorption: Inorganic.—Interrelation of calcium and magnesium absorption was investigated by Alcock and MacIntyre (782). Normal rates of absorption of water, sodium, and potassium in man and animal have been investigated (783). The influence of osmolarity on water and electrolyte flux rates in the duodenum, jejunum, ileum, and colon was explored; net flux of sodium ions and chloride ions in the dog ileum was found to be entirely due to diffusion (784). Edelman described a four-component system for the transfer of water and sodium in blood and tissues (785), and Ginsburg discussed the equilibration of potassium in blood and tissues (786).

Numerous publications appeared on the subject of iron absorption. Cantrill and Walsh (787, 788) and Cantrill, *et al.* (789), investigated iron absorption from the intestinal tract. Brise (790, 791) and Brise and Hallberg (792–795) studied various aspects of iron absorption using radioactive iron-55 or iron-59. Absorption of radioactive iron from segments of the duodenum and ileum of dogs was studied (796). Kinetics of iron absorption in mice has been investigated (797). The effects of oral iron and pregnancy on the active transport of iron by the intestine were reported (798), and Manis and Schachter described a two-step mechanism for the active transport of iron by the intestine (799). Other investigators discussed the role of the duodenum in iron absorption (800). Evidence of serosal "absorption" by the small intestine after intraperitoneal iron injections was presented (801). Results of an investigation by Loria, *et al.*, indicated that concurrent administration of sorbital improved iron absorption in man (802). Ferroglycine sulfate was found to have no advantage over ferrous sulfate (803). Radio-iron was used to study iron absorption following rectal administration (804).

PLANT CHEMISTRY[2]

The volume of literature published in this area during 1962 is tremendous. This is not too surprising since such a small percentage of the world's plants have been investigated from a medicinal point of view. References in this area have been divided into two groups. First is a *Phytochemical Investigation* section which is concerned with studies of specific plants and/or alkaloids; second is a section on *Methodology*.

Phytochemical Investigations.—Several methods of presenting the references for this section were considered. A listing of references according to the plant(s) studied was finally adopted. Such a procedure provides easy reference to the work on a particular plant which may be of interest to the individual phytochemist. Table I, therefore, lists alphabetically each

[2] The writer thanks Dr. G. H. Svoboda for many helpful suggestions concerning the preparation of this section.

TABLE I.—PHYTOCHEMICAL INVESTIGATIONS

Plant	Reference
Acrospira asphodeloides	(805)
Allium sativum	(806)
Amphipterygium adstringens	(807)
Anabasis articulata	(805, 808)
Anabasis setifera	(805)
Angelica edulis	(809, 810)
Arachis hypogaea	(811)
Argemone mexicana	(812)
Aristolochia triangularis	(813)
Artemisia annua	(814)
Artemisia vulgaris	(815)
Aspergillus terreus	(816)
Athyrium mesosorum	(817, 818)
Baccania cordata	(819)
Balanops australiana	(820)
Bersama abyssinica	(821)
Caccinia glauca	(822)
Calophyllum inophyllum	(823)
Casearia sylvestris	(813)
Cassia auriculata	(824)
Cassia goratensis	(824)
Catalpa ovata	(825)
Catha edulis	(826)
Cestrum parqui	(827)
Chenopodium ambrosioides	(828)
Claviceps species	(829)
Cochlospermum gossypium	(830)
Corydalis incisa	(831–834)
Corydalis solida	(835)
Cynanchum caudatum	(836, 837)
Datura species	(838–842)
Daucas carota	(843)
Decodon verticillatus	(844)
Digitalis species	(845–850)
Dryopteris barbigera	(851)
Dryopteris cochleata	(851)
Erysimum diffusum	(852)
Ficus religiosa	(806)
Geissospermum vellosii	(853)
Genista raetam	(854)
Ginkgo biloba	(855, 856)
Ginseng	(857, 858)
Haloxylon salicornicum	(854)
Helenium species	(859, 860)
Leonurus sibiricus	(861, 862)
Leucojum aestivum	(863)
Liriodendron tulipifera	(864)
Litsea japonica	(865)
Lobelia species	(866, 867)
Lopharia papyracea	(868)
Lychnis alba	(869)
Lycopodium species	(870–873)
Magnolia coco	(874)
Magnolia kachirachirai	(874)
Marsdenia tomentosa	(875)
Matricaria chamomilla	(876)
Menispermaceae alkaloids	(877–881)
Metaplexis japonica	(882)
Michelia alba	(883)
Michelia compressa	(884–887)
Mollugo nudicaulis	(888)
Ornithogalum umbellatum	(889)
Orixa japonica	(890)
Papaver species	(891, 892)
Pancratium maritimum	(854)
Pancratium sickenbergeri	(854)
Phegopteris polypodioides	(893)
Pinus species	(894, 895)
Pisum sativum	(896)
Pteryxia terebinthina	(897)
Rauwolfia species	(898, 899)
Rhamnus alaternus	(900)
Rivea corymbosa	(901)
Schinopsis balansae	(813)
Schinus terebinthefolius	(902–904)
Serratia plymuthicum	(905)
Sinapis alba	(906)
Swartzia madagascariensis	(805)
Thalictrum actaefolium	(907)
Thalictrum thunbergii	(908–911)
Tillandsia usneoides	(912)
Tylophora crebriflora	(913)
Veratrum grandiflorum	(914)
Veratrum stamineum	(915)
Vinca major	(916)
Vinca rosea (*Catharanthus roseus*)	(917–920)
Wrightia tinctora	(921)

plant studied, followed by an appropriate reference to the bibliography.

Methodology.—For the purpose of this review, a rather broad interpretation of the subsection title is necessary. While it is intended to be a section primarily concerned with phytochemical methodology, a few references which would not fit conveniently into the preceding sections were included.

A general review of the technology and chemistry of alkaloids was published by Poisson (922). Other investigators studied the preparation of a dry extract of belladonna (923) and the action of boric acid and some of its polyhydroxy complexes on plants (924). Three publications on essential oils discussed such topics as methods of separation, production, composition, and industrial mechanization (925–927). Natural plant hydrocolloids were the subject of three papers by Meer and Meer; origin, physical chemistry, and applications of several gum and gumlike materials were discussed (928–930). Differential studies on plant gums have also been reported (931). Saiki considered the application of statistics to the field of plant internal morphology (932–934). Statistical evaluation of two parameters permitted the classification of Japanese aconites into five types. Two papers dealt with the adsorption of extracted materials on powdered herb residues (935) and the adsorption of ergot alkaloids on activated charcoal (936).

Tissue culture has been successfully used in the field of plant chemistry. Babcock and Carew initiated cultures of callus tissue from several species of *Apocynaceae* (937). In another paper, Staba studied nutritional requirements in tissue cultures of *Digitalis lanata* and *D. purpurea* (938). As part of a study on enzymatic and nonenzymatic oxidation of therapeutically active plant substances, the oxidation of pyrocatechols by peroxydase was investigated (939). Another report dealt with conditions for precipitation of alkaloids

and synthetic bases with Reinecke salt (940). Ali and Guth explored the possibilities of freeze-drying water infusions of alkaloid-containing drug plants (941).

Drug extraction with isopropyl and ethyl alcohols has been reviewed (942). One investigator described an enzymatic procedure for the extraction of alkaloids from *Rauwolfia serpentina* (943), while another studied the dynamics of extraction of rutin from *Sophora japonica* (944). Better extraction and less solvent loss resulted from the application of centrifugal force to the extraction of plant materials (945). Kubiak explored the effect of ultrasonics on the quantitative and qualitative results of plant extraction (946). The ultrasonic energy appeared to increase the extraction of active materials with no decomposition. The action of ultrasound on alkaloids has also been investigated (947).

Several papers were published in the past year on the use of chromatography in phytochemical studies. Farnsworth and Euler reported an alkaloid-screening procedure utilizing thin-layer chromatography (948). Thin-layer chromatography was also used for separation of the active principles of *Ammi visnaga* and *Ammi majus* (949). Sjoholm employed a two-dimensional thin-layer chromatography technique for studying some digitalis glycosides (950). A new solvent system was recommended for the paper chromatography of some veratrum alkaloids and their derivatives (951). Ascending chromatography on a hydrophobic paper was used in a study of the constituents of *Cannabis sativa* (952), and Meer, *et al.*, reported a rapid method which utilizes an ascending paper chromatography technique for the identification and evaluation of botanical extracts (953). Other investigators discussed chromatographic evaluation of glycoalkaloids in *Solanum aviculare* (954). Paper chromatography was also used in a study of the hydrolysis of some alkaloid esters; R_f values for several alkaloids and their hydrolysis products were reported (955).

EQUIPMENT

Automation in the pharmaceutical industry was the subject of several papers published last year. One reported on the automated production of aspirin (956), while two others discussed automation in antibiotic and vitamin manufacturing (957, 958). Automatic coating of tablets was studied (959), and Gabrysh, *et al.*, described an automatic rotational viscometer and high pressure apparatus for the study of non-Newtonian systems (960). Dunlop discussed the mechanization of tablet and capsule packaging (961). In another paper, Schroeter, *et al.*, presented an apparatus for automated dissolution rate studies of capsules and tablets (962).

A review of grinding and pulverizing equipment was published (963). In a series on small-scale processing machinery, Fowler discussed mixers for powders and semisolids (964, 965). A flow-ultramicroscopic method of determining the number concentration and particle-size analysis of aerosols and hydrosols was described (966). Another group of investigators also reported a particle-size analyzer for aerosols (967). An electronic-microscopic method for precise size measurement and analysis of particulate pharmaceutical materials was published by Barnett and Timbrell (968).

Recent advances in freeze-drying were reviewed by Greaves (969). The application of spray-drying techniques to the production of anti-anemia concentrates was also reported (970). Muller discussed rotation viscometers and their application to non-Newtonian measurements (971), and Fairgrieve developed a thermostated bath for viscometry (972). A modified dual-unit organ bath for isolated tissues was also described (973). Continuous recording methods for measuring perspiration were reported by O'Malley (974) and Marchisotto (975).

An apparatus for testing the resistance to wet heat of bacterial spores on paper carriers was described (976). Preparation of sterile ophthalmic solutions in the pharmacy was the subject of an article by Putney (977). A small-scale sterilization apparatus was made by an adaptation of a 5-ml. syringe (978). Three papers were published on the properties of filter materials (979–981). Wolffgang described a simple apparatus for rapid dialysis of small samples (982), and Hart presented some general considerations to aid in centrifuge selection (983). A comparison of Bittel and Cornish systems for separation of stereoisomers by countercurrent distribution was also published (984).

CONCLUSION

The scope of the literature covered in this review is an indication of the complexity of pharmaceutical research today. As pharmaceutical research becomes even more complex in the years ahead, the pharmaceutical scientist will be increasingly dependent on developments in other disciplines. An up-to-date knowledge of the literature provides a sound basis for interdisciplinary communication.

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[3] *Index Medicus* abbreviations were used for journals not listed in *Chemical Abstracts*. In a few instances where the writer was unable to obtain late 1962 issues, references were obtained from *Current Contents*.

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