ABSTRACTS OF PAPERS PUBLISHED IN OTHER JOURNALS

CHEMISTRY

ANALYTICAL

Erythromycin, Infra-red Determination of. W. H. Washburn. (*J. Amer. pharm. Ass., Sci. Ed.*, 1954, **43**, 48.) Samples were assayed by determining the absorption of a chloroform solution containing about 30 mg. of erythromycin per ml. Absorption bands having maxima at 7·29, 9·02, 9·88 and 10·46 μ were investigated, and the results obtained from measurements at 10·46 μ approached most closely a straight line relationship between concentration and absorption, and gave results agreeing most consistently with the microbiological assays, using *B. subtilis* as test organism. The results, calculated from a standard curve prepared from measurements on pure erythromycin, were reproducible within 1 per cent. G. B.

Essential Oils, Oxidimetric Determination of, in Drugs. H. Flück and F. Hoffman. (*Sci. Pharm.*, 1953, **21**, 318.) The method is based on distillation of the drug with brine, and heating the distillate with chromic acid-sulphuric acid in a sealed tube, followed by titration of the excess of chromate. The factor used must be obtained by experiments with known quantities of the essential oil in question. The method is carried out on quantities of 0·05 to 1 g. of the drug. The authors treat in detail the various factors involved in the light of over 3000 determinations which they have carried out. Owing to the range of the results (up to $\pm$ 12 per cent.) the method is not suitable for standardisation of drugs, but is valuable when only a small quantity of material is available. G. M.

Morphine and Codeine, Spectrophotometric Determination of. W. A. Clarke and A. J. McBay. (*J. Amer. pharm. Ass., Sci. Ed.*, 1954, **43**, 39.) Quantitative determinations of codeine and morphine may be carried out rapidly by measuring the ultra-violet absorption at 285 mμ of solutions of *p*H 2. Alternatively, solutions of *p*H 12 may be employed, measurements being made at 298 mμ for morphine or 284 mμ for codeine. Results calculated from absorption data are as accurate as those obtained by using a standard preparation and making a calibration curve. The shift of the absorption maximum of morphine from 285 mμ in acid solutions to longer wavelengths in the presence of alkali serves to distinguish morphine from codeine, the ratio absorption 285 mμ/absorption 310 mμ being greater than 1 for codeine and less for morphine, and the proportion of the alkaloids may be calculated by using 2-component system equations.
G. B.

Phenobarbitone Preparations, Ultra-violet Spectrophotometric Determination of. L. N. Mattson. (*J. Amer. pharm. Ass., Sci. Ed.*, 1954, **43**, 22.) The determination depends on measurements of the optical density of solutions in borate buffer, *p*H 9·5, at 240 mμ and calculation of the quantity of phenobarbitone from the datum $E^{1\ \text{per cent.}}_{1\ \text{cm.}} = 459$. Tablets were powdered, shaken with buffer solution, allowed to stand and filtered. An aliquot quantity of the filtrate was further diluted and the optical density measured against a blank consisting of buffer solution. The method was found to

be rapid and to give results in satisfactory agreement with the U.S.P. method. Stearates did not interfere. Elixir of phenobarbitone was assayed by determination of the absorption at 240 mμ, using a blank of elixir base to compensate for the absorption due to amaranth. For the assay of capsules of ephedrine sulphate and phenobarbitone, the sample was dissolved in a 2 per cent. solution of sodium hydroxide, the ephedrine being extracted with ether and titrated with sulphuric acid. Since the alkali changes the absorption characteristics of phenobarbitone, results calculated from the optical density of the alkaline solution of phenobarbitone were erroneous. More accurate results were obtained by dissolving a sample in borate buffer, measuring the absorption at 240 mμ and correcting for the absorption due to ephedrine sulphate, calculated from the value $E^{1\ \text{per cent.}}_{1\ \text{cm.}} = 3{\cdot}32$.

G. B.

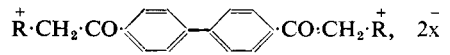
Total Nitrogen, Estimation of, using the Conway Micro-diffusion Cell. E. I. Short. (*J. clin. Path.*, 1954, **7**, 81.) Satisfactory recoveries are achieved from urea solution, serum and urine, with samples as small as 0·05 ml. The sample is heated gently for 5 minutes with 0·5 g. of potassium sulphate, 0·5 ml. of sulphuric acid and 0·03 ml. of a saturated solution of copper sulphate, allowed to cool and 0·3 ml. of a 0·06 per cent. solution of selenium dioxide added. The mixture is boiled gently for 1 hour and 0·375 ml. of a 40 per cent. solution of sodium hydroxide is added and water to 10 ml.; 0·5 or 1·0 ml. of this solution is placed in the outer compartment of a Conway micro-diffusion cell, the inner compartment of which contains 2·0 ml. of a solution prepared by dissolving 5 g. of boric acid in a mixture of 200 ml. of water and 10 ml. of ethanol, adding methylene blue/methyl red indicator solution and diluting to 1000 ml. with water. The lid, coated with white soft paraffin, is placed on the dish, 1·0 ml. of a saturated solution of potassium metaborate added to the outer compartment through a small aperture which is immediately closed and the liquids in the outer compartment mixed by gentle rotation. After a minimum period of 2 hours, required for complete absorption of the liberated ammonia by the boric acid solution, the liquid in the central compartment is titrated with 0·02N hydrochloric acid, to a faint but definite pink colour, using a micrometer syringe which delivers 0·001ml. with an accuracy of ± 0·00005 ml. G. B.

GLYCOSIDES, FERMENTS AND CARBOHYDRATES

***Digitalis purpurea* and *Digitalis lutea* L., Effect of Freeze-drying on the Glycosidal Content of.** F. P. Cosgrove and E. P. Guth. (*J. Amer. pharm. Ass., Sci. Ed.*, 1954, **43**, 90.) Leaves were collected from first and second year plants of *Digitalis purpurea* and second and third year *D. lutea* and dried either at 50° C. for 36 hours or from the frozen state before being ground to powder. The drying methods yielded powders of comparable moisture content. With the exception of those derived from second year plants of *D. purpurea*, freeze-dried samples showed a lower content of total glycosides than oven-dried samples when tested by a modified Knudson-Dresbach colorimetric method. There was no difference in biological activity between oven- and freeze-dried samples as assessed by the frog heart method. It is suggested that heat and enzymatic action break down primary glycosides into secondary glycosides and aglycones during oven drying, the latter giving rise to more colour in the Knudson-Dresbach method. G. B.

ORGANIC CHEMISTRY

Cholinesterase Inhibitors, A New Series of. J. P. Long and F. W. Schueler. (*J. Amer. pharm. Ass., Sci. Ed.*, 1954, **43**, 79.) A series of 11 diphenylamine derivatives was prepared, of the type indicated below, where R contains a quaternary ammonium group and x is Cl, Br or I.



The majority of the compounds were obtained by dissolving $\alpha\alpha'$-dibromo-4:4'-biacetophenone in boiling dioxan, adding the required tertiary amine, allowing to stand for 30 minutes, recrystallising and drying *in vacuo*. The pyridyl and α- and β-methyl pyridyl compounds were as potent inhibitors of bovine erythrocyte cholinesterase as neostigmine bromide (manometric method). Gut stimulation parallelled the *in vitro* cholinesterase inhibiting activity. The more potent cholinesterase inhibitors produced marked potentiation of the depressor response to acetylcholine. Since the derivatives varied widely in activity, a potent anticholinesterase (R = pyridyl), a compound of low potency (R = dimethyl-β-hydroxyethylammonium) and a substance of intermediate activity (R = *N*-ethylpyridyl) were selected for testing on the isolated heart. In this case the potentiation of acetylcholine appeared to run parallel to *in vitro* anticholinesterase activity. G. B.

Streptothricin. Preparation, Properties and Hydrolysis Products. H. E. Carter, R. K. Clarke, Jr., P. Kohn, J. W. Rothrock, W. R. Taylor, C. A. West, G. B. Whitfield and W. G. Jackson. (*J. Amer. chem. Soc.*, 1954, **76**, 566.) Streptothricin is a basic antibiotic with an empirical formula of about $C_{20}H_{34}N_8O_9$ possessing high antibacterial activity. It is tribasic and titration data indicate the presence of three groups with *p*Ka' values of 7·1, 8·2 and 10·1. Analysis disclosed the absence of *O*-methyl, *C*-methyl and *N*-methyl groups. Streptothricin gave positive Pauly, biuret and ninhydrin tests, and amino groups were liberated during hydrolysis, indicating the probability of a peptide structure. The products of acid and alkaline hydrolysis were investigated. On hydrolysis, it yielded ammonia, carbon dioxide and three ninhydrin-positive components, none of which gave significant ninhydrin-carbon dioxide values. One of these products was identified as β:ϵ-diaminocaproic acid. A large scale carbon chromatogram is described which conveniently affords pure sulphates or hydrochlorides of streptothricin or streptomycin. A. H. B.

BIOCHEMISTRY

GENERAL BIOCHEMISTRY

***Streptomyces erythreus*. Isolation of a Second Crystalline Antibiotic from.** C. W. Pettinga, W. M. Stark and F. R. Van Abeele. (*J. Amer. chem. Soc.*, 1954, **76**, 569.) The application of paper chromatographic methods to aid in the isolation and fractionation of erythromycin gave evidence that more than one antibiotic substance could be produced by certain strains of *Streptomyces erythreus*. When grown on a variety of media, these strains were shown to produce erythromycin B in addition to erythromycin. The isolation of erythromycin B was accomplished by use of chromatography on powdered cellulose and countercurrent distribution. It is similar to erythromycin in most of its physical and

chemical properties. Electrometric titration in 66 per cent. dimethylformamide-water showed a titratable group with a *p*Ka′ of 8·5. The molecular weight is 736± 36; specific rotation at 25° C. (2 per cent. in ethanol) was − 78° and m.pt. 191 to 195° C. The infra-red absorption spectrum in methanol is recorded. The microbiological spectrum of erythromycin B is similar to that of erythromycin; however, erythromycin B is only about 75 to 80 per cent. as active. A. H. B.

BIOCHEMICAL ANALYSIS

Ascorbic Acid and Trace Elements, The Effect of, on Vitamin B_{12} Assays. E. M. Stapert, E. B. Ferrer and L. Stubberfield. (*J. Amer. pharm. Ass., Sci. Ed.*, 1954, **43**, 87.) Solutions of cyanocobalamin (vitamin B_{12}) were mixed with ascorbic acid, traces of copper, etc., and assayed microbiologically by a modification of the U.S.P. method. The results were confirmed by saturating the solutions of vitamin B_{12} with ammonium sulphate, extracting with *n*-butanol, separating the butanol solution, extracting with water and calculating the vitamin B_{12} content from the absorption at 361 mμ. None of the added substances alone affected the potency of vitamin B_{12}, but combinations of ascorbic acid with traces of copper, molybdate, fluoride or manganous ions caused some loss of potency. Copper was effective at a concentration of 0·1 p.p.m. and the loss was greater in solutions containing an appreciable proportion of hydroxocobalamin (vitamin B_{12b}). Potassium cyanide and sodium diethyldithiocarbamate, which form complexes with copper, prevented the destruction of vitamin B_{12} activity. G. B.

Catechol Amines in Suprarenal Glands, Estimation of. R. Cass and G. B. West. (*Arch. int. Pharmacodyn.*, 1953, **95**, 283.) Extraction of catechol amines from guinea-pig suprarenals by three methods (acidulated ethanol, 5 per cent. trichloracetic acid, or 0·01 N hydrochloric acid) and estimation biologically, colorimetrically and chromatographically yield values for the total catechol amine content of 121 μg./g. of suprarenal weight. Of this only 3 per cent. is noradrenaline. Both estimates are considerably less than those found by von Euler and Hokfelt (*Brit. J. Pharmacol.*, 1953, **8**, 66) and suggest a real difference between British and Swedish guinea-pigs. It was found that the total catechol amines could be suitably estimated biologically by all three extraction methods. Chromatographic estimation could be used for adrenaline estimation in hydrochloric acid extracts or noradrenaline estimation on concentrated acid ethanol extracts. The noradrenaline content of the concentrated acid ethanol extracts could also be estimated colorimetrically. Hydroxytyramine, dihydroxyphenylalanine, dihydroxyphenylserine, *p*- and *m*-hydroxyphenyl-ethanolamine and tyramine were not detected in any extract. G. P.

Iron and Copper in Serum, Determination of. S. Ventura and J. C. White. (*Analyst*, 1954, **79**, 39.) A method is described for the determination of iron and copper in single samples of serum; the metals are liberated from the proteins with 6 N hydrochloric acid and are determined photometrically as the 2:2′-dipyridyl-ferrous complex and as copper diethyldithiocarbamate, the latter being extracted into a mixture of ether and amyl alcohol. Details of the various stages, including the effect of hydrochloric acid concentration, the precipitation and separation of the proteins, and the formation of the iron and copper complexes are given. Recoveries of iron added to serum ranged from 96·9 to 101·0 per cent.; in the case of copper 93·0 to 101·0 per cent. recovery was obtained.

R. E. S.

CHEMOTHERAPY

Ganglionic Blocking Agent, Synthesis and Evaluation of a New. F. W. Schueler and H. H. Keasling. (*J. Amer. pharm. Ass., Sci. Ed.*, 1954, **43**, 98.) β-Bromopropionyl chloride was heated with ethylene bromohydrin under a reflux condenser and the product, after allowing to stand overnight and removing hydrogen chloride by means of a current of air, was purified by distillation *in vacuo*, and allowed to stand with a large excess of triethylamine. β-Triethylammonium-(β′-trimethylammoniumethyl) propionate dibromide, $(C_2H_5)_3\overset{+}{N}\cdot CH_2\cdot CH_2\cdot CO\cdot OCH_2\cdot CH_2\cdot\overset{+}{N}(C_2H_5)_3$, $2\overset{-}{Br}$, was filtered off and air dried until free from the odour of ether or triethylamine. The substance shows some chemical resemblance to both hexamethonium and muscarinic compounds and might be expected to act as a ganglionic blocking agent, free from side effects such as constipation and mydriasis due to depression of parasympathetic tone. In pharmacological experiments, the substance antagonised ganglion stimulation due to tetramethylammonium or to acetylcholine liberated through reflex stimulation, and did not depress heart rate or amplitude nor affect the coronary flow. Depression of the contraction of isolated intestine or of responsiveness to acetylcholinic stimulation was not observed. The muscarine-like activity seemed to be only sufficient to overcome the loss in parasympathetic tone which accompanied the ganglion-blocking properties. G. B.

PHARMACY

NOTES AND FORMULÆ

Neomycin Sulfate (*New and Nonofficial Remedies, J. Amer. med. Ass.*, 1954, **154**, 338.) Neomycin is an antibiotic isolated from culture media upon which *Streptomyces fradiæ* has grown. It is not inactivated by exudates, enzymes or gastro-intestinal secretions. Neomycin sulphate is a thermostable, polybasic compound soluble in water but insoluble in organic solvents. It is stable for at least 2 years at room temperature. Solutions retain their potency for at least one year at room temperature although the colour may darken; storage in refrigerators is recommended. Neomycin sulphate is very stable and very active in alkaline solution. It is active against Gram-positive and Gram-negative organisms. Of the former it appears more active against staphylococci than streptococci. It has a wider range of activity than bacitracin, penicillin, or streptomycin, and is sometimes effective against pseudomonas and proteus infections; resistant strains have not yet been demonstrated clinically. It is used locally as an ointment or a solution in the treatment or prevention of infections of the skin and eye, including impetigo, wounds, burns, ulcers, conjunctivitis, blepharitis and sty. Local therapy may be supplemented by administration of sulphonamides or penicillin. Blood levels of 0·2 mg. per ml. or more may produce serious kidney damage. Neomycin should not, therefore, be given parenterally or in high and prolonged oral dosage. It may be used in divided total daily oral dosage not exceeding 6 to 10 g. for one to three days for suppression of the bacterial flora in surgery of the large colon and anus. It has a mild laxative effect after oral administration but is otherwise usually well tolerated. G. R. K.

PHARMACOGNOSY

***Digitalis orientalis*, A Preliminary Phytochemical Investigation of.** D. H. Gregg and O. Gisvold. (*J. Amer. pharm. Ass., Sci. Ed.*, 1954, **43**, 106.) An aqueous extract of the leaves of *Digitalis orientalis* was treated with methyl *iso*butyl ketone and the extract separated into ether-insoluble and ether-soluble fractions. The ether-soluble material was separated by chromatography on an aluminium oxide column, using chloroform, chloroform/ethanol mixture and ethanol as solvents. Acetyldigoxin, amorphous *digitalinum verum* and other amorphous glycosides were obtained from the various fractions. Solvent mixtures were devised for the separation of digoxin, acetyldigoxin and lanatoside C by ascending or descending paper chromatography, but no satisfactory separation of digitoxin, acetyldigitoxin and acetyldigoxin was effected. A suitable test for glycosides may be carried out as follows. Dry the glycosidal material on filter-paper, spray with a 1 per cent. solution of hydrogen chloride in methanol to which has been added 0·5 ml. of a 10 per cent. ferric chloride solution per 100 ml. Dry rapidly under an infra-red lamp, under conditions which avoid charring of the paper. A blue-grey colour indicates the presence of glycosides. This test detects the sugar moiety, giving a positive result for digitoxose, sucrose, fructose and sorbose, but if the genin is present the spot fluoresces in ultra-violet radiation. The fluorescence test is sensitive to about 0·6 μg. of glycosides. By the application of a periodate-benzidine test it was deduced that the glucose residue of lanatoside C and the terminal glucose digitoxose residue of digitoxin, digoxin and gitalin are in the pyranose form and that the acetyl group in the cardiac glycosides of digitalis is on the terminal digitoxose residue. G. B.

PHARMACOLOGY AND THERAPEUTICS

Adrenal Steroids, Corticotrophin and Growth Hormone, Effect of, on Resistance to Experimental Infections. E. H. Kass, M. M. Lundgren and M. Finland. (*J. exp. Med.*, 1954, **99**, 89.) Large doses of adrenocorticotrophin or of cortisone depress resistance to infections. Experiments are reported on the survival of mice injected with a blood culture of a mouse virulent strain of pneumococcus or with mouse adapted influenza A virus and treated with cortical hormones. Cortisone, in doses of 5 mg. for 5 days, diminished the LD50 of pneumococci about tenfold. Administration of a single dose of 5 mg. depressed resistance significantly, and the effect persisted between 3 and 6 days suggesting a slow rate of absorption. Corticotrophin, in doses from 0·3 to 20 mg., had no significant effect on resistance or survival time. Hydrocortisone in the form of free alcohol depressed resistance, but the effects of the acetate were variable, probably due to variable rates of hydrolysis in the tissues. Growth hormone in large doses acted like cortisone and when given with cortisone did not overcome the effect. Similar results were obtained with influenza virus, cortisone and hydrocortisone depressed resistance while corticosterone had possibly no effect. The rate of multiplication of viral particles in infected mouse lungs, when determined by titration in embryonated eggs, showed a rapid multiplication during the first 2 days followed by a distinct fall by the sixth day. The cortical hormones did not alter the rate of accumulation of the virus, but the decline in the titre values was slower than with the controls. G. F. S.

Aminopentamide, Pharmacological Activity of. J. B. Hoekstra, D. E. Tisch, N. Rakieten and H. L. Dickison. (*J. Pharmacol.*, 1954, **110**, 55.) Aminopentamide, DL-$\alpha\alpha$-diphenyl-α-dimethylaminovaleramide (centrine), is a potent antispasmodic with atropine-like properties. On the isolated guinea-pig and rabbit ileum strips it has approximately half the activity of atropine and 1/5 the activity of papaverine in relaxing spasms induced by acetylcholine, barium chloride and histamine. In dogs, it decreases the tone and activity of the stomach and intestinal tract and relaxes spasms produced by acetylcholine, arecoline and pilocarpine. It does not completely block the action of histamine. Aminopentamide is nearly as effective orally as intravenously or intramuscularly. On the colon of the normal dog it is more effective and of longer duration than either atropine or banthine. Contractions of the bladder are also reduced and the spasmogenic actions of histamine arecoline and acetylcholine blocked. It is slightly less active than atropine in blocking the vasodepressor responses to acetylcholine and arecoline, and only 1/4 as active as atropine in blocking the effects of vagal stimulation of the heart. Aminopentamide has less mydriatic effect and is less effective than atropine in antagonising the stimulant action of pilocarpine on salivary flow. Daily doses up to 50 mg. have been given to dogs over 2 months without producing any gross or microscopic abnormalities.

G. F. S.

Atropine and Methylatropine, Ganglionic Blocking Action of. L. D. Fink and P. Cervoni. (*J. Pharmacol.*, 1953, **109**, 372.) Methylatropine, a quaternary nitrogen compound, has been compared with atropine and tetraethylammonium for ganglionic blocking activity. Experiments were carried out in anæsthetised cats, transmission through the cervical ganglion following preganglionic stimulation being determined by measuring the response of the nictitating membrane. The drugs were given intravenously and the dose determined which caused a 50 per cent. decrease in the contraction of the nictitating membrane. In 5 experiments this dose was 0·19 mg./kg. for methylatropine, and 1·0 mg./kg. for tetraethylammonium, methylatropine being therefore approximately 5½ times as active as tetraethylammonium on a weight basis and approximately 8 times as active on a molar basis. The duration of action was from 3 to 6 minutes for each compound. With atropine large doses reduced the response to postganglionic stimulation and corrections were necessary for this. It was found that 3·9 mg./kg. of atropine was equal to 0·8 mg./kg. of tetraethylammonium or, atropine had one-fifth the activity of tetraethylammonium and one-fifteenth to one-twentieth the activity of methylatropine. Methylatropine, tetraethylammonium and atropine blocked the carotid sinus vasopressor reflex produced by bilateral occlusion of the common carotid arteries, and also from the ganglionic stimulating drug 1 : 1-dimethyl-4-phenylpiperazium iodide. Again methylatropine was the most potent and atropine the least potent compound. G. F. S.

***Caulophyllum thalictroides*, a Pharmacological Study of a Crystalline Glycoside of.** H. C. Ferguson and L. D. Edwards. (*J. Amer. pharm. Ass., Sci. Ed.*, 1954, **43**, 16.) Oil was removed from powdered rhizomes and roots of *Caulophyllum thalictroides* (blue cohosh) by extraction with ether, and the residue extracted with hot ethanol. The solution was evaporated to a reddish-brown extract which was mixed with pumice, sand and water and filtered to extract alkaloids. The residue, dissolved in ethanol was decolourised with charcoal and the solution evaporated. The product was treated with cold dehydrated ethanol to remove impurities and recrystallised from ethanol to give white crystals of a

glycoside, melting point 255° to 256°C. An aqueous solution, prepared with the aid of sodium hydroxide was used for pharmacological tests. It was shown to cause construction of the coronary vessels of the rat's heart and of the carotid arteries of cattle and hogs. The substance exhibited a spasmogenic action on the isolated intestine of the rat, guinea-pig, mouse and rabbit and a pituitary-like effect on the rat uterus. Concentrations greater than 0·01 per cent. caused hæmolysis in the rabbit. The LD50 by intravenous injection was 11·8 mg./kg. for mice and 20·3 mg./kg. for rats. The substance was very irritant when injected into the ear or instilled into the cornea of the rabbit. G. B.

Chloramphenicol, Blood Dyscrasias Associated with. R. Hodgkinson. (*Lancet*, 1954, **266**, 285.) Details are given of 31 instances of blood dyscrasias after the administration of chloramphenicol, of which 28 were aplastic anæmia and 3 granulocytopenia. In 26 of the 28 patients with aplastic anæmia there were hæmorrhagic manifestations such as severe epistaxis, hæmoptysis, bleeding from the gums, hæmatemesis, spontaneous bruising, and petechial hæmorrhages. Reduction of the red-cell, white-cell and platelet counts occurred; in 22 persons the sternal marrow was examined and showed scanty red-cell and white-cell precursors with an increased proportion of lymphocytes. 24 of the 31 instances have so far proved fatal, 4 have recovered and 3 are being maintained by blood transfusions, The immediate cause of death in many cases was internal hæmorrhage; liver damage, except for fatty degeneration in 2 persons, was mentioned in only one post-mortem report. A heavy total dose for an adult, assuming treatment for a week, would be 26 g. Of 19 adults in the series, 16 received a total of more than 26 g. and the average quantity taken by the 14 patients whose total dose is known was more than 60 g. 3 received less than 26 g., one receiving only 1 g. of chloramphenicol and 75 mg. of pyribenzamine one week before the onset of aplastic anæmia. Of the 11 children in the series, 5 received more than double the maximum total dose that should be given having regard to age. In 8 of the 11 treatment was maintained for more than 24 days. The author suggests that chloramphenicol should not be given for chronic conditions, that the total dosage should not exceed 26 g. in adults or the equivalent of 100 mg./kg. of body weight daily for 7 days in children, and that the length of treatment should not exceed 10 days. H. T. .B.

Chlorpromazine, Anti-emetic Activity of. E. D. Brand, T. D. Harris, H. L. Borison and L. S. Goodman. (*J. Pharmacol.*, 1954, **110**, 86.) Chlorpromazine, 10-(γ-dimethylaminopropyl)-2-chlorophenothiazine, is a new drug related to promethazine, but it shows no antihistamine properties and is used for sedation. In dogs it has been found to be effective in antagonising apomorphine-induced vomiting, while promethazine is inactive. It protects against vomiting induced by morphine and ergot, but it is ineffective against intravenous copper sulphate, lanatoside-C, veratrum and oral copper sulphate. In cats chlorpromazine does not prevent vomiting induced by apomorphine, lanatoside-C and intravenous copper sulphate. In dogs therefore it blocks only drugs affecting the medullary emetic chemoreceptor trigger-zone, whereas it does not in cats. The results appear to be due to a species difference. G. F. S.

Chlorpromazine, Mechanism of Therapeutic Action. P. Decourt. (*Thérapie*, 1953, **8**, 846.) Chlorpromazine has two important pharmacological actions, an adrenergic blocking action and a "narcobiotic" action (this term being introduced by the author to embrace the direct depressant effects of the drug

on cellular metabolism). Comparative pharmacology on the one hand and analysis of the multiple effects of the drug in mammals on the other show this narcobiotic action to be the one mainly—perhaps exclusively—concerned in the therapeutic action of chlorpromazine. The comparative studies were carried out on the seed of a higher plant, *Lepidium sativum*, on a unicellular organism of the genus *Infusoria*, *Tetrahymena piriformis*, on a microscopic fungus, *Sterigmatocystis nigra*, and on some *Streptococci*. In each case there was a striking correlation between the narcobiotic action of members of the phenothiazine group of drugs and their relative central depressant action in man. Similarly 933F (piperoxane) and 883F (prosympal) which have an adrenergic blocking action equal to that of chlorpromazine, have a much feebler narcobiotic action. Conversion of the tertiary base to the corresponding quaternary compound greatly diminishes the narcobiotic action. The link between the lower organisms, where the narcobiotic effects were measured by their immersion in a solution of the drug, and mammals, where the drug was injected, was provided by the dogfish, *Scyllium canicula*. Here the drug was administered by both means and results comparable with both groups obtained. In higher animals such as the mammal where central co-ordination involves a great number of cellular elements, even a slight narcobiotic effect can be sufficient to involve complex nervous networks such as the reticular formation and the hypothalamic centres in what appears at first sight to be a selective depression. In actual fact the fractional depression of each neurone summates with its successors to raise the excitatory threshold. This explains why conditioned reflexes are more easily depressed by chlorpromazine than are simple reflexes. The narcobiotic action is suggested as being related to an anti-diastatic action, but evidence is not conclusive. G. P.

Chlorpromazine, Studies on the Adrenergic Blocking Properties of. P. Marquardt. (*Thérapie*, 1953, **8**, 787.) In the cat, chlorpromazine in a dose sufficient to cause complete reversal of the vasopressor response to intravenous adrenaline, has little effect on the action of noradrenaline. The reversal of adrenaline is one criterion of the degree of activity of a drug to be used in "hibernation anæsthesia" since this condition appears to depend mainly on a blocking of the emergency sympathetic reflexes recruited in the body during the induced hypothermia. The ideal dose of chlorpromazine in man would be one where there is blockade of the adrenaline vasopressor response without reversal. Where there is reversal of the response there is an acute danger of circulatory collapse. G. P.

Cortisone Acetate and *p*-Aminobenzoic Acid in Long Term Treatment of Rheumatoid Arthritis. L. L. Wiesel and A. S. Barritt. (*Amer. J. med. Sci.*, 1954, **227**, 74.) The synergistic action of sodium or potassium *p*-aminobenzoate and cortisone acetate, both compounds being given orally, was investigated in 31 patients during periods of a year or more. 23 of the patients were given large doses of cortisone acetate alone for 1 to 2 weeks at the commencement of treatment after which the dose was reduced to 37·5 mg. daily in 3 divided doses. As soon as relapse was obvious, 30 to 45 ml. of a 10 per cent. solution of sodium or potassium *p*-aminobenzoate was given 1 hour before each dose of cortisone. In 22/23 patients this combined treatment was as effective as the large doses of cortisone acetate, while in the other patient improvement was much greater on cortisone alone. The remaining 8 patients were given the combined treatment only and their improvement was satisfactory. 2 patients developed a toxic drug

rash due to the *p*-aminobenzoate after 12 and 13 months respectively and treatment had to be discontinued. Some gain in weight occurred but the age-height-weight ratios remained within normal limits and, rarely, there was a mild rounding of the face, but no other signs of hypercorticoidism were encountered; no euphoria occurred. Patients have been maintained on the combined treatment for periods up to 3 years without any of the serious side effects of cortisone becoming apparent. In severe cases maximal improvement was not reached until treatment had continued for 60 to 90 days. The cause of the synergism is under investigation; it appears to be connected with the inhibiting effect of *p*-aminobenzoic acid on the destruction of cortisone by liver tissue. H. T. B.

Diphenhydramine, A New Group of Sedatives Related to. W. Weidmann and P. V. Petersen. (*J. Pharmacol.*, 1953, **108**, 201.) A series of 37 compounds, closely related to diphenhydramine, have been studied for sedative, convulsant, spasmolytic and toxic properties. Sedative action was determined in mice, the movements of which were measured in an activity cage and the dose producing sedation in 50 per cent. of the animals (SD50) was determined. Convulsant action and toxicity were also determined in mice, and spasmolytic action on the isolated guinea-pig ileum. For the antihistamine antagonists the SD50 could be determined only for promethazine, since diphenhydramine mepyramine and tripelennamine showed only excitatory actions which apparently masked any sedative actions. The compounds showed qualitatively similar properties to diphenhydramine but quantitatively there were considerable differences. They showed a considerable loss of antihistamine activity *in vitro*, stronger sedative actions, and much stronger spasmolytic activities against barium chloride. A comparison between the sedative and spasmolytic effects showed no systematic relationship between the members of the series and there was no relationship between the sedative effect and histamine antagonism. G. F. S.

Disodium Calcium Ethylenediamine Tetra-acetate, Enhancement of Lead Excretion by. M. Rubin, S. Gignac, S. P. Bessman and E. L. Belknap. (*Science*, 1953, **117**, 659.) Ethylenediamine tetra-acetic acid (versene), a synthetic chelating agent, forms strong un-ionised soluble chelate complexes with cations, especially those of the di- and trivalent types. In animals and humans, when administered intravenously in large doses over short periods, it lowers the systemic calcium level, forming a calcium chelate. The calcium in this complex may be displaced by other metals and is non-toxic. This paper reports that the administration of the calcium complex causes a marked enhancement of lead excretion in patients with acute lead poisoning. G. F. S.

Isoniazid; Tubercle Bacilli Resistant to. D. A. Mitchison. (*Brit. med. J.*, 1954, **1**, 128.) Eight pairs of sensitive and resistant strains of tubercle bacilli were obtained from the sputum of 8 patients in the Medical Research Council (1952) trials of isoniazid. The sensitive strains were obtained before treatment with isoniazid, and the resistant strains were obtained during or up to 3 months after treatment with isoniazid. The virulence and response to treatment of these strains were then investigated on guinea-pigs. It was found that the higher the degree of resistance of a strain the lower was the virulence to guinea-pigs. Treatment with isoniazid in a dose comparable to that used in man (i.e. 4 mg./kg./day by subcutaneous injection) protected animals infected with sensitive strains, and partially protected animals infected with a resistant strain growing on Lowenstein medium containing isoniazid 0·2 μg./ml. but not on

1 μg./ml. It did not protect animals infected with resistant strains growing on 1 μg./ml. and, indeed, may have increased the virulence of some of these strains. S. L. W.

Nalorphine Hydrobromide, Treatment of Acute Heroin Intoxication. M. Strober. (*J. Amer. med. Ass.*, 1954, **154**, 327.) A 22-year-old mulatto woman suffering from the effects of an unknown overdose of heroin was comatose on admission to hospital, with respiratory arrest and pin-point pupils. She was promptly placed in a respirator but no improvement occurred. The patient appeared lifeless. She was then given 5 mg. of nalorphine intravenously. Within one minute she began to breathe, her pupils dilated, and she rapidly became conscious and sat up. She then became belligerent. G. R. K.

α-(2-Piperidyl)benzhydrol Hydrochloride, A New Central Stimulant, Pharmacological Studies on. B. B. Brown and H. W. Werner. (*J. Pharmacol.*, 1954, **110**, 180.) Central stimulation by α-(2-piperidyl)benzhydrol hydrochloride is characterised with small doses by a marked reduction in reaction times to environmental stimuli and by continuous very rapid, but highly co-ordinated movements in experimental animals. With increasing doses duration of hyperactivity is increased more than is the degree of activity. Lethal intravenous doses and oral doses cause tremors and convulsions, and death occurs by respiratory depression during convulsions, with the exception of oral administration in dogs and subcutaneous administration in rats, where death occurs suddenly in the state of hyperactivity. The new stimulant differs from amphetamine in inducing hyperactivity without signs of increased irritability and anorexia. Also toxic doses of amphetamine cause depression after first convulsing; this depression was absent after convulsions with the new drug. The drug antagonises light to moderate degrees of depression with barbiturates, but not lethal barbiturate depression which in some cases was increased so that death occurred earlier. Here it again differs from amphetamine which has little analeptic action with light degrees of barbiturate depression and from leptazol which antagonises lethal barbiturate depression. Also, in contrast to leptazol and amphetamine, lethal doses of the new stimulant are not antagonised to any appreciable extent by the barbiturates. The drug has little vasopressor activity. In the low decerebrate cat there is a stimulation of the righting reflexes. G. P.

Primidone (Mysoline) and Phenobarbitone, Effects of Liver Damage and Nephrectomy on Anticonvulsant Activity of. E. W. Swinyard, D. H. Tedeschi and L. S. Goodman. (*J. Amer. pharm. Ass., Sci. Ed.*, 1954, **43**, 114.) Tests for anticonvulsant potency were carried out by the method of maximal electroshock seizures in rats. The anticonvulsants were administered orally as a 10 per cent. suspension in gum acacia solution, so as to permit tests to be carried out at the time of maximum liver damage, 36 to 48 hours after the injection subcutaneously of 2 ml./kg. of a 50 per cent. solution of carbon tetrachloride in arachis oil, or 12 hours after nephrectomy. Liver damage increased the anticonvulsive potency by an average of 50·7 per cent. for primidone (5-phenyl-5-ethylhexahydropyrimidine-4:6-dione) and 63·7 per cent. for phenobarbitone, and increased the duration of action fourfold for primidone and threefold for phenobarbitone. Nephrectomy markedly increased the effect and duration of action of primidone, but did not significantly alter the effect of phenobarbitone. It is suggested that in the rat, both liver and kidneys are important in the degradation and elimination of primidone, whereas the liver rather than the kidneys is reponsible for the removal of phenobarbitone. G. B.