ABSTRACTS OF PAPERS PUBLISHED IN OTHER JOURNALS

CHEMISTRY

ANALYTICAL

Chloramphenicol, Colorimetric Determination of. F. M. Freeman. (*Analyst*, 1956, **81**, 299.) The method depends upon the formation of a stable red colour resulting from interaction of the nitro group with a dimethylformamide-acetone solution in the presence of tetraethylammonium hydroxide. To 10 ml. of dimethylformamide is added 0·2 ml. of 0·1 per cent. solution of acetone in dimethylformamide and 0·1 ml. of a 25 per cent. solution of tetraethylammonium hydroxide in water. After mixing, 0·1 to 0·15 mg. of chloramphenicol in dimethylformamide is added, the tube shaken and the absorption at 520 mμ measured after 10 minutes using a 1-cm. cell and a reagent blank. D. B. C.

Chlorinated Organic Pesticides, Separation and Identification of. L. C. Mitchell. (*J. Ass. off. agric. Chem., Wash.*, 1956, **39**, 484.) A procedure is described by which the following chlorinated pesticides may be identified and separated by paper chromatography: Aramite (2(*p-tert.*-butylphenoxy)*iso*-propyl-2-chloroethylsulphite), captan (*N*-trichloromethylmercapto-4-*cyclo*hexene-1 : 2-dicarboximide), dieldrin(1 : 2 : 3 : 4 : 10 : 10-hexachloro-6 : 7-epoxy-1 : 4 : 4a : 5 : 6 : 7 : 8 : 8a-octahydro-1 : 4-endo, exo-5 : 8-dimethanonaphthalene), Gamma benzene hexachloride, Spergon (chloranil : 2 : 3 : 5 : 6-tetrachloro-1 : 4-benzoquinone), and tritisan (pentachloronitrobenzene). The solvent systems recommended are acetic anhydride 20 per cent. in ether as immobile solvent and *n*-heptane as mobile solvent, or refined soyabean oil 5 per cent. in ether as immobile solvent and 95 per cent. ethanol as mobile solvent. The two systems did not separate the 6 pesticides in the same order. With acetic anhydride-*n*-heptane the ascending order was captan, Spergon, Aramite, gamma benzene hexachloride, dieldrin and tritisan; with oil-ethanol it was tritisan, Spergon, dieldrin-gamma benzene hexachloride, Aramite and captan. Several chromogenic agents were used and the relative merits of each are discussed. The R_F values for the pesticides in either of the solvent systems are given and it is shown that the 6 compounds can be identified in mixtures by the order of separation and the distances from one another. B. A. W.

Lobeline, Determination of. E. Steinegger and F. Ochsner. (*Pharm. Acta Helvet.*, 1956, **31**, 65.) Lobelia herb may contain up to 20 bases, and chromatographic separation of the lobeline is essential. The total alkaloids are first determined, and this operation may be carried out with 1·2 g. of the drug if 0·01N solutions are used. For the chromatography 9 ml. of formamide is shaken with anhydrous ammonium formate and treated with 20 ml. of acetone. The excess of formate is filtered off, and 1 ml. of concentrated formic acid is added. The paper is saturated with this mixture, and hung up to drip and evaporate. The mobile phase is composed of 9 volumes of chloroform and 1 volume of benzene. A test is run with pure lobeline, followed by a little of the mixture, as the presence of other compounds modifies the R_F value. This spot is made visible with Dragendorff's reagent. The lobeline to be determined is extracted, using the method of the authors (*Pharm. Acta Helvet.*, 1955, **30**, 345) and the extinction is determined at 245 mμ. A blank is done

from a strip of the chromatogram cut out at the same height. Examples of results obtained are given below:

	L. salicifolia	*L. inflata*
Total alkaloids per cent. ..	1·388	0·342
Lobeline per cent.	0·17	0·03

G. M.

Nux Vomica Tincture, Simplified Assay for. M. Scott, A. Taub and C. Piantadosi. (*J. Amer. pharm. Ass., Sci. Ed.*, 1956, **45**, 232.) The method depends upon the treatment of a sample of tincture with aluminium oxide which absorbs pigments, followed by absorption of the alkaloids on an ion exchange resin, subsequent elution and estimation of strychnine and brucine by ultra-violet spectrophotometry. 10 g. of aluminium oxide is stirred with 5 ml. of tincture and 5 ml. of ethanol (70 per cent.) for 5 minutes, allowed to stand and filtered. The aluminium hydroxide is washed with quantities of ethanol (70 per cent.) and the washings mixed with the filtrate and made up to 50 ml. 10 ml. of this solution is adjusted to pH 9–10 with ammonia solution, mixed with 10 ml. of specially prepared and purified resin (Amberlite IRC–50(H)), the liquid filtered off and the resin washed. The alkaloids are extracted from the resin by heating at 80° C. with successive quantities of 25 ml. of 0·1N hydrochloric acid in ethanol (70 per cent.) and the extracts diluted to 100 ml. This solution, after suitable dilution with water is clarified by filtration through a porous crucible and the absorbance determined at 255 and 264 mμ, using a blank prepared as above, taking 5 ml. of ethanol (70 per cent.) instead of the tincture. The quantity of strychnine and brucine present is calculated by means of simultaneous equations. The method is rapid and gives results in agreement with the U.S. National Formulary assay. G. B.

***Rauwolfia serpentina* Preparations, The Chemical Evaluation of.** J. Carol, D. Banes, J. Wolff and H. O. Fallscheer. (*J. Amer. pharm. Ass., Sci. Ed.*, 1956, **45**, 200.) The following method is recommended for the determination of reserpine and rescinnamine, the constituents of *Rauwolfia serpentina* which are chiefly responsible for the hypotensive and sedative effects of the drug. Preparations of powdered root, extracts and tablets are extracted and the fraction containing reserpine and rescinnamine is separated by partition chromatography on a Celite column using an ethanolic citrate buffer solution as the immobile solvent and a mixture of *iso*-octane, chloroform, water and ethanol as the mobile solvent. The solution containing reserpine and rescinnamine is evaporated and hydrolysed in alcoholic sodium hydroxide solution by heating on a water bath for 20 minutes. Trimethoxybenzoic and trimethoxycinnamic acids are extracted from the solution by acidifying and shaking with chloroform, and the light absorption of the chloroform solution is determined at 270 and 300 mμ. The quantities of trimethoxybenzoic and trimethoxycinnamic acids, and hence of reserpine and rescinnamine are calculated after determination of the absorbancies of solutions of the pure acids in chloroform. The method appears to be satisfactory for commercial preparations, although in one case interference was caused by the dye from the coating of a tablet and in another by an emulsifying agent present in the preparation. For the identification of *Rauwolfia serpentina* preparations, two methods of ascending paper chromatography are proposed. One requires the use of a mixture of heptane, carbon tetrachloride and formamide as mobile solvent in an atmosphere of ammonia. The other, which permits the separation of alkaloids of relatively high R_F

value, depends on the use of a mixture of benzene, *iso*-octane and formamide. A large number of fluorescent spots are obtained in these tests, and no other species of *Rauwolfia* produces all of them. G. B.

Tyrothricin, Nephelometry in Assay of. S. Leclercq. (*J. Pharm. Belg.*, 1956, **11**, 33.) *Streptococcus faecalis* M19 or *Staphylococcus aureus* 209P or Oxford may be used as the test organism, special precautions being necessary to ensure that the culture employed is in the logarithmic growth phase. Solutions of a standard preparation of tyrothricin are prepared to contain 0·033, 0·05 and 0·075 μg./ml. in a mixture of propylene glycol 43·75 ml., water 43·75 ml. and ethanol (95 per cent.) 12·5 ml. Similar dilutions are prepared from the sample under examination, and tubes of the test culture are inoculated with 1 ml. of the tyrothricin solutions. 8 tubes are inoculated for each concentration of the standard, and 6 for each concentration of the unknown. The tubes are incubated at 37° C., 2 tubes of each concentration of the standard being used as pilot tubes, the turbidity being measured at intervals until the change in turbidity is proportional to the logarithm of the concentration and the slope of the turbidity/log. concentration graph is sufficient to give a high precision. Growth in all tubes is stopped by adding 2 drops of formaldehyde solution. The turbidities in the tubes are measured, and the concentration of tyrothricin calculated. The assay is sensitive and good precision may be achieved. It is not affected by the usual quantities of quaternary ammonium compounds such as cetrimide which may be present in pharmaceutical preparations of tyrothricin. G. B.

ORGANIC CHEMISTRY

Cephalosporin C, Degradation of. E. P. Abraham and G. G. F. Newton. (*Biochem. J.*, 1956, **62**, 658.) Cephalosporin C was rapidly hydrolysed at pH 12 with loss of activity and of the absorption maximum at 260 mμ. Back titration after 2 hours at pH 12 showed that two new acidic groups had been formed. The solution gave a positive nitroprusside test, but titration failed to reveal the presence of a new group with a pK indicative of a simple thiol. Alkaline hydrolysis with barium hydroxide (0·3N; 100° C.; 2 hours) followed by paper ionophoresis, showed the formation of glycine and α-aminoadipic acid. Cephalosporin C treated with cephalosporinase gave an acid, with loss of the absorption maximum at 260 mμ. Hydrolysis in N hydrochloric acid at 105° C. gave carbon dioxide, a volatile base (2 equivalents), D-α-aminoadipic acid, and traces of glycine, whilst hydrolysis of dinitrophenylcephalosporin C gave dinitrophenyl α-aminoadipic acid, indicating the presence of a D-α-aminoadipic acid residue with a free amino group. The pK (9·8) of the amino group in cephalosporin C was very close to that of the amino group of α-aminoadipic acid, suggesting that the α-carboxyl group of this residue is also free in cephalosporin C. Hydrogenation of cephalosporin C at a palladium-charcoal catalyst gave a product which retained the ultra-violet absorption at 260 mμ, but only 10 per cent. of the antibacterial activity of cephalosporin C. Hydrolysis of this material with dilute acid at 105° C. gave α-aminoadipic acid and glycine. Treatment of the hydrolysate with bromine yielded a small quantity of substance, which when chromatographed on paper behaved as penicillaminic acid. Hydrogenolysis with Raney nickel and acid hydrolysis of the product gave D-α-aminoadipic acid, valine, L-alanine and glycine, and in this respect cephalosporin C resembles the penicillins. The dinitrophenyl and benzyl derivatives of cephalosporin C are more active against *Staph. aureus* and less active against *Salm. typhi* than the parent compounds. J. B. S.

BIOCHEMISTRY

BIOCHEMICAL ANALYSIS

Chlorpromazine, Colorimetric Estimation of. H. Leach and W. R. C. Crimmin. (*J. clin. Path.*, 1956, **9**, 164.) A rapid and sensitive method is described for the estimation of chlorpromazine in blood and urine. For extraction from urine, add 1 ml. of N sodium hydroxide to 20 ml. of urine, extract four times with 20 ml. portions of ether and wash the pooled extracts with 10 ml. 0·2N sodium hydroxide followed by 10 ml. of water. Remove the wash water completely and shake the extract vigorously with 0·1N sulphuric acid. Stand for five minutes, remove the acid extract, warm slightly and aerate to remove traces of ether. Take duplicate 4 ml. quantities for the estimation. For free chlorpromazine in blood, heat 5 ml. of oxalated blood with 5 ml. of 50 per cent. potassium hydroxide for two minutes on a boiling water bath. Cool, add 10 ml. of water, shake with 20 ml. ether and remove the ether layer. Repeat the extraction three times. Wash the pooled ethereal extracts with sodium hydroxide and water, extract with 6 ml. of 0·1N sulphuric acid and take 4 ml. of the acid extract for colour development. For extraction of total chlorpromazine in blood, heat 5 ml. of blood and 5 ml. of concentrated hydrochloric acid in a boiling water bath for five minutes. Cool, make alkaline and extract with ether as for chlorpromazine. For the estimation treat 4 ml. samples with 2 ml. of 50 per cent. sulphuric acid and mix well. Add 0·2 ml. of a solution of 2 per cent. ferric nitrate in 1·0N sulphuric acid and read the colour at 530 μ (Ilford spectrum green filter 604) against a water blank. Obtain the result from a standard calibration curve. At least 90 per cent. of chlorpromazine added to urine could be recovered down to 1·0 mg. per litre. G. F. S.

Mercury in Biological Materials, Microdetermination of. F. R. Barrett. (*Analyst*, 1956, **81**, 294.) A method is described suitable for quantities up to 20 μg. with a sensitivity of 0·5 μg. of mercury, and for handling quantities up to 20 g. of blood or tissue. A modified digestion procedure is described which ensures complete destruction of organic matter with moderate heating so that no mercury is lost. The tissue is digested with an appropriate amount of a mixture of equal parts of concentrated sulphuric and nitric acids under a cold-finger condenser for 2 hours after foaming has ceased. The bulk of fatty material is then filtered off through glass wool. Potassium permanganate is added in the form of 0·5 g. tablets and the mixture heated until a precipitate of manganese dioxide persists after boiling. It is then diluted with water and further tablets added while boiling until a pink colour persists and any fatty material has been oxidised. After decolorisation with hydroxylamine hydrochloride, the solution or an aliquot of it is extracted with a solution of dithizone in chloroform (6 mg. per litre) and the chloroform extracts washed with 0·25N sulphuric acid and then extracted with a mixture containing 10 ml. of a 40 per cent. solution of potassium bromide and 50 ml. of 0·25N sulphuric acid. This latter extract, containing mercury as K_2HgBr_4, is brought to a pH of about 6 with a buffer containing disodium hydrogen phosphate and sodium carbonate and extracted with exactly 10 ml. of dithizone reagent which is separated and filtered through a plug of absorbant cotton wool. The absorption of the solution at 490 mμ is measured. A blank must be carried through the whole process. Practical results are given which show that good recoveries of mercury added to blood and liver samples are obtained. The preliminary extraction of the metal is claimed to minimise interference from copper and other heavy metals. D. B. C.

PHARMACY

NOTES AND FORMULAE

Digitalis Leaf, Stability of. R. A. Sachs, J. D. Highstrete and M. L. Pabst. (*J. Amer. pharm. Ass., Sci. Ed.*, 1956, **45**, 250.) The potency of a sample of digitalis was determined by the U.S.P. XIV pigeon method, and re-determined at intervals of 12, 18 and 24 months. The initial potency was 17·4 units/g., and there was a significant loss during the first 12 months' storage, the potency then averaging 13·5 units/g. No further loss in potency was observed during the following 12 months. The samples were stored in the form of whole leaf and in powder, in metal containers at room and refrigerator temperatures, and in paper sacks and cardboard containers at room temperature. There was no significant difference in stability between whole and powdered leaf, but samples stored in sealed metal containers retained their potency better than those stored in paper sacks or cardboard containers. There appeared to be no advantage in storing the metal containers in a refrigerator. G. B.

Erythrocyte-Glycerol Mixtures; Preparation for Transfusion. H. A. Sloviter and R. M. Tietze. (*Amer. J. med. Sci.*, 1956, **231**, 437.) Erythrocyte-glycerol mixtures which have been thawed after prolonged storage at low temperatures cannot be transfused directly because of the osmotic lysis of the hypertonic erythrocytes which would occur. A simple method is described whereby the osmotic lysis is prevented and the erythrocytes are relatively rapidly prepared for transfusion. To the thawed erythrocyte-glycerol mixture is added concentrated glucose solution (50 g. of glucose and 0·9 g. of sodium chloride per 100 ml.) in the proportion of 50 ml. of glucose solution per 100 ml. of thawed mixture. After standing for 10 minutes at room temperature the mixture is quickly diluted with twice its volume of 0·9 per cent. sodium chloride solution. The resulting suspension of erythrocytes contains approximately 4·5 per cent. glycerol and 5·5 per cent. glucose in addition to the electrolyte, and has a total osmotic pressure about 4 times that of blood plasma. *In vitro* experiments simulating the osmotic forces which occur during transfusion showed the feasibility of the method from the osmotic point of view. It was shown that 85 per cent. of the original numbers of erythrocytes remained intact after prolonged storage, processing and simulated transfusion. Transfusion studies in man are now in progress. S. L. W.

Oil-in-water Emulsions, The Formation of, with Ultrasonic Vibrations. J. Mounier, P. Blanquet, G. Piffault and G. Dallies. (*Bull. Soc. Pharm. Bordeaux*, 1955, **94**, 161.) Experiments were carried out with an ultrasonic generator tuned to 958, 576, 320 and 288 kc/s. With radiation of constant strength, an oil-in-water emulsion was formed which fairly rapidly became richer in oil until a constant value was reached. Emulsions formed at any of the above frequencies were very stable and were not destroyed by another of those frequencies. The rapidity with which the oil was emulsified was dependent on the viscosity of the oil, castor oil and liquid paraffin being less rapidly emulsified than olive and sweet-almond oils, but was independent of the chemical nature of the oil. Particles of oil in the emulsions appeared to be spherical, 0·5 to 4 μ in diameter, but larger particles appeared when high intensities of radiation were used and foaming was allowed to occur. Of the oils examined, only sweet-almond showed any chemical change during the treatment with ultrasonic radiation. In this case the iodine value fell from 75 to 51. G. B.

PHARMACOLOGY AND THERAPEUTICS

Carbutamide in the Treatment of Diabetes. A. S. Ridolfo and W. R. Kirtley. (*J. Amer. med. Ass.*, 1956, **160**, 1285.) This is a report on the compound carbutamide, 1-butyl-3-sulphanilylurea (BZ–55). Carbutamide is rapidly absorbed when administered by mouth; within 30 minutes after a single 2·5 g. dose there is an appreciable concentration in the blood. Maximum values (10–15 mg. of free sulphonamide per 100 ml. of whole blood) are reached within 3 to 6 hours, and the blood level falls slowly after 6 to 7 hours. Within 2 to 3 hours after ingestion of a dose of 2·5 g. a definite lowering of blood sugar level occurs. Excretion is relatively slow; the drug is found in the urine with approximately 66 per cent. as the free form and 33 per cent. as the acetylated form. The substance does not have an action equivalent to injected insulin; to be effective, some insulin must be present, either endogeneous or injected. Carbutamide was administered to 31 diabetic patients. Satisfactory responses were achieved with an average loading dose of 2·5 g. the first day, 1·5 g. the second day, and 1 g. daily thereafter; attempts were made to maintain a level of at least 10 mg./100 ml. of blood. This trial showed that carbutamide will effectively lower the blood sugar level in many patients with mild or moderately severe diabetes, and in some cases may enable them to dispense with insulin. Carbutamide cannot be used in the emergency treatment of a diabetic with acidosis, nor is it satisfactory in young persons with unstable diabetes; in this respect it is not an insulin substitute. Those responding favourably to the drug are those who become diabetic in maturity, are obese or overweight and have not required an excessive dose of insulin. Only one patient out of 31 showed any toxic effects, a skin rash and leucopenia, which developed after 3 months on a dose of 1 g. daily; these conditions cleared up on discontinuation of therapy. The toxicity of the drug appears to be low, but since the mechanism of action is not yet known it should be used with caution. S. L. W.

Methylserotonins as Potent Antimetabolites of Serotonin. E. N. Shaw and D. W. Woolley. (*J. Pharmacol.*, 1956, **116**, 164.) The serotonin-like and anti-serotonin activities of several alkyl-substituted serotonins were estimated *in vitro* on sheep carotid artery segments and on oestrogenic rat uteri, and *in vivo* on the blood pressure of anaesthetized dogs. Anti-serotonin activity was expressed as an inhibition index, being the amount of analogue required to prevent the effect of a unit weight of serotonin, usually measured after one minute exposure to the analogue. The inhibition indices for 2:5-dimethylserotonin were 10 for arterial segments, and 100 to 1000 for the uterus, the latter becoming 10 to 20 after 20 minutes exposure to the antagonist. The antagonist had no serotonin-like activity on the arterial segments and little on the uterus. On the blood pressure, however, about 1 mg./kg. i.v. of the dimethylserotonin caused a rise, the response to subsequent doses of serotonin being considerably modified: the pressure rise was abolished and the initial fall in pressure became very prominent and persistent, even where previously the initial fall had been absent. Large intravenous doses of serotonin protected against a subsequent injection of the unit dose, through tachyphylaxis, but compared with the anti-serotonin activity of 2:5-dimethylserotonin, the effect was short-lived, recovery being full after one hour. Orally 2:5-dimethylserotonin was about 10 times less effective than by injection. 1:5-Dimethylserotonin had marked serotonin-like activity, being 1/10 to 1/5 as active as serotonin on the uterus and 1/10 on blood pressure: anti-serotonin activity was less than that of 2:5-dimethylserotonin. The inhibition indices of other serotonin derivatives on the rat uterus

were: 1-benzyl-2:5:-dimethylserotonin, 30; 1-benzyl-5-methylserotonin, 40; 1:2:5-trimethylserotonin, 200; 2:5-dimethylserotonin on this tissue having an index of 300. The increase in potency with the benzyl compounds was associated with irreversible inhibition by the compounds, which may explain the high activity. The 1-benzyl-2:5-dimethyl derivative was also the most effective orally in antagonizing the serotonin pressor response in the dog. Toxicity of the compounds in mice was low. G. P.

Morpholinoethylnorpethidine, Analgesic and other Properties of. A. F. Green and N. B. Ward. (*Brit. J. Pharmacol.*, 1956, **11**, 32.) Determination of the analgesic action of this compound in the rat by heat and tail pressure methods have shown it to have an activity intermediate between morphine and pethidine. The compound was capable of giving as great an elevation of the pain threshold as morphine. The LD50 by the intravenous route in mice was 45 mg./kg., and the main toxic action was respiratory depression, which paralleled analgesic activity. The action of the compound on the cough reflex in cats, on rectal temperature in rabbits and on heart rate and pupil diameter in dogs also resembled those of morphine. It abolished the peristaltic reflex of the isolated guinea-pig ileum and caused defaecation in dogs. Like morphine it produced excitement in cats. The effects of the compound were antagonised by nalorphine. G. F. S.

Motion Sickness, Evaluation of Drugs for Protection Against. (*J. Amer. med. Ass.*, **1956, 160,** 755.) The results are recorded of a trial of a number of drugs against motion sickness. These included diphenhydramine, meclizine, 1-diethylamino-2-(2′-benzyl-4′-chlorophenoxy) ethane (BL-717), dimenhydrinate, cyclizine, ethopropazine, promethazine, pyrathiazine, scopolamine hydrobromide and pheniramine. Other compounds given preliminary screening included calcium pantothenate, nicotinamide, pyridoxine and thiamine, and the antihistamines *N*-benzhydryl-*N*-*m*-methylbenzyl-piperazine, buclizine (Vibazine) hydrochloride, β-diethylaminoethylphenothiazine-10-carboxylate (Transergan), phenyltoloxamine (Bristamin), and 1-methyl-4-amino-*N*′-phenyl-*N*′-(2′-thenyl)-piperidine tartrate (Sandostene); antispasmodics such as benztropine (Cogentin) methanesulphonate, scopolamine methobromide (Pamine bromide); and tranquilizers such as chlorpromazine (Thorazine), reserpine (Serpasil), and the alseroxylon fraction of *Rauwolfia serpentina* (Rauwiloid). The drugs were tested on service personnel in transport ships of the same type on the Atlantic crossing during the autumn and winter months. All medicaments and a placebo were supplied in pink capsules to ensure identical appearance, and the capsules were swallowed under observation. Vomiting was the sole criterion of effectiveness, and the level of significance of each drugs' effectiveness compared with the placebo was determined by a chi-square test. Four regimens, namely, meclizine 50 mg. 3 times daily and once daily, cyclizine 50 mg. 3 times daily, and promethazine 3 times daily, by statistical analysis were more effective than the other treatments tested. Diphenhydramine and dimenhydrinate were identical with the placebo. Reserpine, alseroxylon, and scopolamine hydrobromide, especially the latter when more than a single dose was given, were responsible for numerous distressing side effects. Cyclizine gave significant but not impressive protection when given twice daily and promethazine twice daily was inferior to meclizine once daily; there was no statistical difference between the results of giving meclizine once daily and three times daily. None of the vitamins nor chlorpromazine was of any value. For long sea voyages meclizine is the drug of choice. For shorter voyages, a single dose of meclizine, cyclizine or promethazine should be equally effective. H. T. B.

Noradrenaline in the Adrenals of Young Dogs. T. Ozaki. (*Tohoku J. exp. Med.*, 1956, **63**, 241.) Extracts of the adrenal glands of young dogs were made in 4 per cent. trichloroacetic acid and the adrenaline and noradrenaline content estimated by the permanganate method. It was found that in dogs of 2–7 days there was a mean of 64 per cent. noradrenaline, in dogs of 20–30 days 42 per cent. noradrenaline, while in adult dogs a value of 18·5 per cent. noradrenaline was found. This is similar to results obtained in guinea-pigs, rabbits and cats. M. M.

Novobiocin, Laboratory and Clinical Evaluation. F. Lin and L. L. Coriell. (*Antibiotic Med.*, 1956, **2**, 268.) Data are presented that show that novobiocin is bacteriostatic in low concentration (0·19 to 50 μg./ml.), and bactericidal in higher concentration (200 to 400 μg./ml.), being intermediate in this respect between penicillin and erythromycin. Very high blood levels are obtained promptly following oral dosage, adequate levels persisting for at least 8 hours. Every one of 22 strains of *M. pyogenes* var. *aureus* isolated from patients was found sensitive to novobiocin; 19 out of the 22 were resistant to penicillin, 12 were resistant to chloramphenicol and 5 to erythromycin. Resistance to novobiocin developed in a step-like manner similar to that with erythromycin and chloramphenicol. Of 11 strains of micrococci isolated from patients, all became resistant to novobiocin following 12 serial transfers in a sublethal concentration of the drug. The occurrence of cross-resistance with erythromycin, chloramphenicol and penicillin was not demonstrated; several strains actually became more sensitive to penicillin after they became resistant to novobiocin. Novobiocin was used in 12 staphylococcal infections of the skin, respiratory tract, and bone, 3 cases of scarlet fever, and 1 case of cutaneous anthrax. All patients recovered promptly, both clinically and bacteriologically, with the exception of a case of fibrocystic disease of the pancreas with extensive bronchopneumonia. In most cases of pyodermia, abscesses, pneumonia, and osteomyelitis dramatic clinical improvement appeared after 24 hours of therapy. A dose of 5 mg./kg. repeated every 6 to 8 hours was found sufficient in most cases to maintain continuous therapeutic blood levels. The only side-effects noted were an urticarial rash in one patient and diarrhoea in another. S. L. W.

Novobiocin; Plasma and Spinal Fluid Concentrations in Man. G. M. Bayne, S. C. Strickland, J. M. Glyfe and W. P. Boger. (*Antibiotic Med.*, 1956, **2**, 166.) Novobiocin (previously called streptonivicin or cathomycin) is an antibiotic with activity against most of the commonly pathogenic Gram-positive organisms and several Gram-negative organisms. *Micrococcus pyogenes* var. *aureus*, *Corynebacterium diphtheriae*, *Streptococcus pyogenes*, *Diplococcus pneumoniae*, and *Streptococcus agalactiae* are all inhibitied by concentrations less than 5 μg./ml. and *Streptococcus faecalis* by 12·5 μg./ml. Of the Gram-negative organisms *Haemophilus pertussis*, *Pasteurella multocida*, and *Proteus vulgaris* are all sensitive at concentrations less than 10 μg./ml. From a study of 41 individuals given either single or multiple doses of novobiocin, data are presented which indicate that an initial oral dose of 2 g. of novobiocin sodium promptly produced a plasma level averaging 126·8 μg./ml., and subsequent doses of 500 mg. at 12-hourly intervals tended to maintain levels in the range of 20 μg./ml. or greater. Such levels are four or more times greater than those necessary for the *in vitro* inhibition of the common Gram-positive pathogens. In 24 individuals who received single oral doses of novobiocin up to 2 g. none of the antibiotic was assayable in the spinal fluid despite plasma levels up to 90 μg./ml. The samples of cerebrospinal fluid were obtained within 2–7 hours after administration of the dose. None of the patients studied showed any evidence of untoward side-effects with the exception of vomiting in one case. S. L. W.

Novobiocin, Studies on. H. J. Simon, R. M. McCune, P. A. P. Dineen and D. E. Rogers. (*Antibiotic Med.*, 1956, **2**, 205.) The studies reported in this paper indicate that novobiocin possesses a high degree of *in vitro* activity against the Gram-positive cocci. Most strains of staphylococci were found sensitive to low concentrations of novobiocin regardless of their sensitivity or resistance to other antibiotics. Most strains of proteus isolated directly from patients appeared moderately sensitive to novobiocin but all other Gram-negative micro-organisms studied proved resistant. The *in vitro* studies indicated a high degree of serum binding with 90 to 95 per cent. loss of novobiocin activity in the presence of 20 per cent. serum. Such binding is rapidly reversible on simple dilution, and prompt urinary excretion in high concentrations suggests that the novobiocin-protein complex is readily dissociated *in vivo*. Novobiocin at dietary levels of 100 mg./kg. was effective in the treatment of an experimental staphylococcal infection in mice; an experimental proteus infection in mice also responded to treatment. Studies in man indicated that novobiocin is rapidly absorbed from the gastrointestinal tract. High serum concentrations were frequently attained after oral ingestion of the drug, peak concentrations of 25–50 μg. occurring 1 to 6 hours after ingestion of 500 mg., with detectable serum concentrations remaining at 8 hours. Marked variation in serum concentrations and 24-hour urinary excretion was noted, suggesting variation in the degree of intestinal absorption. Ingestion of the drug on an empty stomach produced significant serum concentrations more rapidly than ingestion after meals. Novobiocin did not appear in the cerebrospinal fluid but was found in significant concentrations in pleural and ascitic fluid after an initial time lag. High urine concentrations were achieved following oral administration though only a small fraction of the dose was recovered from the urine in the first 24 hours. No evidence of hepatic, renal, or haemopoietic system toxicity was observed following administration of novobiocin to a small number of patients. S. L. W.

Oxytocin as Stimulator for the Release of Prolactin from the Anterior Pituitary. G. K. Benson and S. J. Folley. (*Nature, Lond.*, 1956, **177**, 700.) The suckling stimulus influences the mammary gland in two ways. First, suckling or other conditioned stimuli can cause the release from the neurohypophysis of oxytocin, which in turn causes the contraction of the myoepithelial cells associated with the alveoli, resulting in ejection of stored milk. Secondly, the suckling stimulus causes the release from the anterior lobe of the pituitary of prolactin which participates in the maintenance of secretion and of the functional integrity of the mammary alveolar tissue. These facts suggest that the primary effect of such impulses is to activate the neurohypophysis, thus causing a release of oxytocin which stimulates the anterior pituitary to release prolactin. In order to test this hypothesis use was made of the fact that the involution of mammae in the lactating rat, the suckling of which is prevented by the surgical removal of the nipples, is retarded provided that suckling of the intact nipples is continued. Studying the effect of injections of oxytocin on the course of mammary involution in lactating rats from which the litters were removed on the fourth day of lactation, it was found that the oxytocin treatment caused marked retardation of mammary involution. Such results indicate that the release of prolactin (and perhaps other anterior-pituitary hormones concerned in lactation) can be stimulated by treatment with oxytocin. It is unlikely that the results are due to a direct effect of oxytocin on the mammary gland. M. M.

Penicillin-Triple Sulphonamide Mixture in Urinary Tract Infections. A. W. Bohne and W. E. Chase. (*Amer. J. med. Sci.*, 1956, **231**, 389.) A clinical

and bacteriological study was conducted in 148 out-patients, of whom 98 per cent. were adult females, to compare the effectiveness of two oral preparations, a triple sulphonamide mixture and a penicillin-triple sulphonamide mixture, in uncomplicated acute and chronic infections of the urinary tract. The triple sulphonamide mixture contained sulphadiazine, sulphamerazine and sulphadimidine, 0·167 g. of each, or a total of 0·5 g./5 ml. in an alumina gel base; the second mixture contained the same amounts of the three sulphonamides plus 150 mg. of benzathine-penicillin G in 5 ml. Microscopic examination and culture of urine specimens before medication demonstrated a variety of organisms, with *E. coli* present in 65 per cent. An initial dose of one or other of the mixtures of 2 g., followed by 0·5 g. 4 times a day was given for 7 days. There was no significant difference in the effectiveness of the two mixtures. Of 71 patients treated with the triple sulphonamides 79 per cent. were freed of urinary infection; of 77 who received the penicillin-sulphonamide mixture 75 per cent. were freed of infection. Both preparations were active against the coccal infections. The triple sulphonamide agent eradicated *Proteus vulgaris* in 6 out of 7 cases. The penicillin-sulphonamide mixture was more effective in preventing secondary growth of organisms not present in pre-treatment cultures. Reactions, including headache, chills, rash, swelling and redness of the tongue occurred in only 3 cases and subsided promptly on withdrawal of medication. There was no evidence of crystalluria and no gastrointestinal disturbances. S. L. W.

Prednisone and Prednisolone in Rheumatoid Arthritis. E. W. Boland. (*J. Amer. med. Ass.*, 1956, **160**, 613.) The effects of prednisone, prednisolone and hydrocortisone were compared in 141 arthritic patients over periods of from 6 to 9 months. None of the cases was mild and the average duration had been 126 months. The drugs were discontinued in 12 cases because improvement was insignificant and/or serious complications intervened. In the moderately severe cases the maintenance doses of prednisone and prednisolone were found to be 5 to 15 mg./day by mouth, indicating that these drugs are about four times as potent as hydrocortisone. Prednisone and prednisolone were found to be interchangeable. The patients were divided into three active groups: (1) those who had never or not recently been on hydrocortisone therapy (32 patients); (2) those whose condition had previously been adequately controlled on hydrocortisone (39 patients); and (3) those whose condition had not been adequately controlled on hydrocortisone (70 patients). In (1), satisfactory levels of improvement were maintained in 19 (59 per cent.); in (2), 38 of the 39 patients maintained adequate improvement; in (3), adequate improvement was maintained in 34 (49 per cent.). Compared with hydrocortisone the advantages of the new drugs are their lack of salt and water retention and absence of potassium loss, their lesser tendency to raise blood pressure, and their ability to restore adequate levels of improvement in a significant number of patients whose arthritis has not been controlled by prolonged administration of hydrocortisone. Their disadvantages consist of a greater proclivity for gastric irritation and demonstrable peptic ulcers, ecchymotic skin lesions, and vasomotor symptoms. Qualitatively they produce the same antirheumatic response but their milligram potency is multiplied. Prednisone or prednisolone are to be preferred when salt and water retention is an actual or potential problem, and in patients who do not respond adequately to the older steroids or who escape control after their prolonged use. On the other hand, hydrocortisone should be preferred in patients with a history of peptic ulcer and gastric irritation from the new steroids. S. L. W.

Sarin and Tabun, Contributions to the Pharmacology of. C. Heymans, A. Pochet and H. van Houtte. (*Arch. int. Pharmacodyn.*, 1956, **104**, 293.) In the anaesthetized dog the anticholinesterases Sarin and Tabun induced bronchospasm, laryngospasm, bradycardia and other manifestations of parasympathetic activity, convulsions and muscular fasciculation. Death resulted from bronchospasm or laryngospasm or from cardiac arrest. Sarin depressed respiration, whereas Tabun caused transient hyperpnoea. Either hypotension or hypertension was produced by both drugs, depending upon whether the main effect was peripheral and hypotensive or central and excitatory on the vasomotor centres. Section of the vagus nerves had no effect on bradycardia or bronchospasm induced by the drugs. Injection of either drug into the circulation of the perfused isolated head, connected to its trunk only by the vagus nerves, did not cause bradycardia; so that, unlike acetylcholine, Sarin and Tabun have no stimulant action on the cardioinhibitory centre. Similarly the two anticholinesterases had no action on carotid chemoreceptors, other than to cause a fleeting hyperpnoea, caused by the cyanide in the Tabun molecule. Ganglion-blocking agents such as tetraethylammonium, hexamethonium and Pendiomid diminished or depressed transitorily the bradycardia induced by Sarin or Tabun. Residual bradycardia was blocked by atropine. The convulsions and muscular fasciculations were also blocked by the ganglion-blocking agents and atropine. Most of the parasympathomimetic actions of Tabun or Sarin were blocked by atropine; the miosis induced by large doses of the anticholinesterases was only influenced slightly, however, by atropine. Death in atropinized dogs was brought about by central or peripheral respiratory collapse. G. P.

Spermine and Spermidine, Pharmacology of. C. W. Tabor and S. M. Rosenthal. (*J. Pharmacol.*, 1956, **116**, 139.) The toxicity of spermine, spermidine, their enzymatic oxidation products and some related aliphatic mono- and diamines was studied in mice and rats. Injected intravenously into unanaesthetized rats, spermine and spermidine in a dose of 0·15 mM/kg. produced a transient histamine-like fall in blood pressure. The same dose given intraperitoneally to rats and mice caused gasping and laboured abdominal respiration (suggestive of bronchoconstriction). In these animals renal insufficiency developed within three to eight days. Like other nephrotoxic agents spermine exerted a diuretic action in mice. Among the other amines examined, nephrotoxic activity was shown by ethyleneimine, bromoethylamine, ethylenediamine and propylenediamine. The results suggested that spermine, spermidine and the above amines owe their nephrotoxic action to formation of reactive and unstable amino-aldehydes. Enzymatic degradation of spermine by beef plasma amine oxidase gave intermediately, spermidine, and finally NH_3, H_2O_2, putrescine, and an amino-aldehyde. The degradation products had no nephrotoxic action in mice. Also, if spermine and amine oxidase were injected separately no significant renal injury resulted. However, injection of the degradation products of spermine directly into the renal artery of a rabbit caused renal damage which indicates that damage after i.v. injection may be the result of degradation of spermine in the high concentration in which it accumulated in the renal tubular epithelium; destruction elsewhere may be the basis for the protection with amine oxidase described above. Amine oxidase had no protective action in renal damage caused by chloroform, mercuric chloride, polymyxin B and alloxan. Spermine or spermidine had no toxic action *in vitro* on spermatozoa, but amine oxidase added with, or incubated previously with, spermine or spermidine increased toxicity greatly. Bactericidal action and to a less degree trypanocidal

(ABSTRACTS *continued on p.* 1175.)

However, the defects of the book are those of its qualities, particularly its comprehensiveness. Too much has been attempted and unfortunately the attempt has succeeded. It is impossible to meet the needs of widely differing kinds of reader and still give full value to each. So large and heavy a publication is not really a practical proposition from the user's point of view and it seems essential in future to issue the book in more than one volume. If the contents of each volume could be selected with the main kinds of user in mind, the student would certainly welcome something more portable and the pharmacist would not have to pay for information he does not require. Yet for those who have the money to spare and want a single reference work on all the subjects that go to make up modern pharmacy, Remington is probably the book of choice.

H. TREVES BROWN.

(ABSTRACTS *continued from p.* 1173.)

action of these amines followed a similar pattern. Some related amines showed no such toxicity. Some sulphhydryl compounds inhibited the toxic action. Spermine had an anti-heparin action and an effect on blood coagulation similar to that of protamine. G. P.

APPLIED BACTERIOLOGY

Mercury Salts, Value of, as Disinfectants and Fungicides for Inanimate Surfaces. L. F. Ortenzio, L. S. Stuart and J. L. Friedl. (*J. Ass. off. agric. Chem., Wash.*, 1956, **39**, 476.) The authors report results obtained when six mercury salts were tested for bactericidal and fungicidal activity. The bactericidal tests were made in accordance with the Association of Official Agricultural Chemists use-dilution method, using *Salm. choleraesuis* and *M. pyogenes* var. *aureus* as the test organisms and using U.S.P. thioglycollate broth as the subculture medium. Tests for fungicidal activity employed the A.O.A.C. fungicide test method, using *Trichophyton interdigitale* and *Streptomyces scabies* as test organisms. The mercurials were found to have much greater fungicidal than bactericidal activities. Thus 1–20 dilutions of mercuric chloride and mercuric potassium iodide were required to kill the two bacteria whereas dilutions of 1–4500 and 1–3500 respectively were effective against the spores of *T. interdigitale*. Phenylmercuric salts were also found to be fungicidal in high dilution. The mercury salts were used in aqueous solutions containing low but unspecified concentrations of acetic acid. Investigations with *Streptomyces scabies* were made in order to determine the behaviour of organisms intermediary between bacteria and fungi. A standardised conidiospore suspension was killed within 10 minutes by 1–80 phenol and by 1–5000 mercuric chloride, indicating that *Streptomyces* are similar to fungi in their sensitivity to mercurials. It is concluded that mercurials might possess value in decontaminating premises or articles carrying causative agents of fungal infections. Although the bacteriostatic and fungistatic activities of mercurials are well-established, the authors point out that, where pyogenic and enteric bacteria are concerned, claims of disinfecting benefits cannot be justified unless the formulation contains bactericidally active chemicals other than mercury salts. B. A. W.