ABSTRACTS OF PAPERS PUBLISHED IN OTHER JOURNALS

CHEMISTRY

ALKALOIDS

Raunescine and *iso*Raunescine from *Rauwolfia canescens* L. N. Hosansky and E. Smith. (*J. Amer. pharm. Ass., Sci. Ed.*, 1955, **44**, 639.) Two new alkaloids were isolated from a weakly basic alkaloidal fraction from which reserpine and canescine had been removed. The material was extracted with ether in the presence of acid and alkali to remove colour and other impurities. Raunescine and *iso*raunescine were then extracted with chloroform and separated on a silica column, by developing first with chloroform and then with chloroform containing 2 per cent. of methanol to obtain raunescine. *iso*Raunescine was obtained by continuing the development with chloroform containing 5 per cent. of methanol. The two alkaloids appeared to be isomeric, and gave ultraviolet absorption spectra almost identical with that of canescine. The infrared spectra were similar, but raunescine showed a doublet at 5·68 and 5·82 μ, in place of the single band at 5·79 μ in the spectrum of *iso*raunescine. As in the case of canescine, there was no absorption band at 6·18 μ, associated with the 11-methoxyl group. It is suggested that these alkaloids possess the same structure as canescine, with a hydroxyl group in place of methoxyl at position 17. G. B.

δ-Yohimbine from the Bark of *Rauwolfia verticillata*. H. R. Arthur. (*Chem. Ind.*, 1956, 85.) A hot methanolic extract from the bark of *R. verticillata* (prepared after initial extraction of the bark with light petroleum) was evaporated to dryness and the green tar which remained was extracted with hot benzene. The residue was triturated with water, the mixture filtered and the filtrate extracted with chloroform. The chloroform was evaporated to dryness and as much as possible of the residue dissolved in benzene and chromatographed on alumina, benzene being used as eluant. The alkaloidal fractions appearing in the eluate were combined and recrystallised from methanol to yield stout needles of δ-yohimbine m.pt. 252 to 253·5° C. A. H. B.

ANALYTICAL

Atropine in Mixtures, Polarographic Determination of. B. Novotný (*Československ. Farm.*, 1955, **4**, 448.) Atropine, which itself is inactive, can be determined polarographically in the form of its nitro derivative. For the determination of atropine in injections containing 0·01 g. of morphine hydrochloride and 0·0005 g. of atropine sulphate per ml., a 2-ml. sample is diluted with 30 ml. of water, 1 ml. of a 10 per cent. potassium hydroxide solution is added, and the mixture is extracted with chloroform. An aliquot of the extract, containing about 250 μg. of atropine, is transferred to a 50-ml. flask and the chloroform is removed in a stream of air. The residue is heated for 30 minutes on a water bath with 1 ml. of concentrated nitric acid and 0·1 ml. of 15 per cent. sulphuric acid. The solution is allowed to cool and 10 ml. of a 20 per cent. potassium hydroxide solution is added; it is then polarographed at 0·0 V., a stream of nitrogen being passed through the cell. A second aliquot of the chloroform extract to which 250 μg. of atropine sulphate has been added is treated in the same way. The atropine content of the sample is calculated with

the aid of a calibration graph constructed from the results obtained by polarographing solutions prepared from 200, 400, 600 and 800 μg. of atropine sulphate. The nitro derivative of atropine gives two waves and the height of the first wave is proportional to the concentration of atropine. E. H.

Bacitracin and Neomycin in Admixture, Determination of. J. Lingnau and G. Machek. (*Sci. Pharm.*, 1955, **23**, 234.) Since bacitracin is used therapeutically as such, while neomycin is employed in the form of sulphate, there is a possibility of separation of these two antibiotics by making use of their differing solubilities in alcohols. It was found that bacitracin is easily soluble, while neomycin sulphate is practically insoluble in ethanol or methanol (about 0·01 to 0·02 per cent. at 37° C.). Alcohols do not destroy the activity of these compounds. For the assay of mixed preparations, the material is extracted with cold ethanol (96 per cent.) and the undissolved neomycin sulphate is assayed microbiologically using *Micrococcus flavus*. The ethanolic solution is diluted with 0·1M phosphate buffer (pH 6) and assayed similarly, using *B. subtilis*. In the case of powders containing phenylmercuric acetate it is possible to determine the neomycin sulphate only. In the case of ointments a preliminary removal of fat by light petroleum is desirable. The results published show satisfactory agreement. G. M.

Benzene Hexachloride, Separation of Isomers of. R. G. Bridges, A. Harrison and F. P. W. Winteringham. (*Nature, Lond.*, 1956, **177**, 86.) Whatman No. 1 filter paper strips were washed with water to remove an inorganic halide contaminant present in the paper, dried, dipped in 5 per cent. w/v solution of white soft paraffin in ether, drained and dried. The mixture of the isomers was applied in acetone solution and the mobile phase consisted of 70 per cent. methanol and 30 per cent. water by volume. Descending chromatography was used at laboratory temperature. After 18 hours the strip was dried and the positions of the isomers was detected by dipping the paper in redistilled mono-ethanolamine, heating at 100° C. for ½ hour and then dipping in 0·1N solution of silver nitrate acidified with concentrated nitric acid (10 vol. silver nitrate solution: 1 vol. acid). On exposure to ultra-violet light, brown spots appeared corresponding to the positions of the isomers. The alpha- beta-, gamma- and delta-isomers moved with mean R_F values of 0·33, 0·00, 0·40 and 0·58 respectively. The method of detection was sensitive to less than 5 μg. of all but the beta-isomer which was only just detectable in 5 μg. quantities. A. H. B.

Chloramphenicol, Periodate Oxidation in the Analysis of. A. Valseth and A. Wickstrom. (*Medd. Norsk. Farm. Sels.*, 1955, **17**, 345.) Hydrolysis of the amide linkage in chloramphenicol yields dichloroacetic acid and an aminodiol (+)-threo-1-(*p*-nitrophenyl)-2-amino-propanediol-1:3, which may be oxidised with periodate to *p*-nitrobenzaldehyde, formaldehyde, ammonia, and probably formic acid. The optimum pH region of the periodate oxidation of the aminodiol was found to range from 7·0 to 7·5. In the presence of a phosphate buffer of optimum pH the periodate uptake of the aminodiol mounted rapidly to the theoretical value of 2·0 molecules and did not exceed this value after one hour. The unused periodate was reduced with sodium arsenite, the excess being titrated against iodine. A method is also described which makes it possible to determine quantitatively 0·2–2 per cent. free aminodiol in chloramphenicol samples (125 mg.): the sample is oxidised with periodate, ammonia originating from any free aminodiol is separated from the reaction mixture by microdiffusion in Conway standard cells and then determined spectrophotometrically by Lubochinsky and

Zalta's modificaion of the colour reaction with phenate-hypochlorite. The amount of free aminodiol liberated from chloramphenicol eye drops by heating to 100° C., was evaluated by titration of the periodate uptake and by micro-determination of the ammonia evolved by oxidation with periodate. After heating at 100° C., for 30 minutes the chloramphenicol was hydrolysed to an extent of 3·8 per cent., the hydrolysis increasing to 15·4 per cent. after 2 hours.

R. E. S.

Disulfiram, Colorimetric Determination of. B. Salvesen and L. Domange. (*Ann. pharm. franç.*, 1955, **13**, 499.) The method depends upon the formation of a yellow colour when a solution of disulfiram is treated with copper. This reaction appears to be specific for the group $=N{\cdot}CS{\cdot}S{\cdot}S{\cdot}CS{\cdot}N=$. To 10-ml. quantities of solutions in acetone of the sample under examination and of known quantities of pure disulfiram (200–1000 μg.) is added 0·45 g. of copper turnings, previously treated with nitric acid and washed with water, ethanol and ether. The colour is developed by allowing the samples to stand for 7 hours with occasional shaking. The colour intensity is measured at intervals and readings are recorded when the maximum intensity is reached. Measurements are made with a photoelectric colorimeter and a screen having a maximum transmission at about 434 mμ. The quantity of disulfiram in the sample under test is read from the standard curve drawn from the figures obtained with the pure samples. Methanol may be used in place of acetone, but 0·2 g. of copper turnings should be used and the maximum colour intensity is obtained after 5 to 6 hours. About 25 hours is required when *cyclo*hexane is used as solvent. G. B.

Erythromycin, Colorimetric Determination of, using Methyl Sulphate. M. Pesez. (*Ann. pharm. franç.*, 1955, **13**, 513.) The following method is recommended. To 2 ml. of solution of erythromycin or erythromycin ethylcarbonate in methylethyl ketone add 8 ml. of methyl sulphate, shake and allow to stand for one hour. Measure the absorption at 480 mμ, by means of a spectrophotometer, and prepare a standard curve for quantities of 50 to 300 μg. of erythromycin. For the assay of tablets of erythromycin, shake a quantity of the powdered tablets equivalent to about 0·1 g. of erythromycin with 25 ml. of methyl ethyl ketone for 15 minutes. Filter, dilute the solution with the same solvent and complete the determination as above. The quantity of erythromycin is read from the standard curve, which is linear for quantities of 50 to 300 μg. G. B.

Glycyrrhizic Acid in Succus Liquiritæ, Determination of. H. Onrust, A. P. Jansen and B. S. J. Wöstmann. (*Rec. Trav. chim. Pays-Bas.*, 1955, **74**, 1515.) Glycyrrhizic acid is a glycoside composed of glycyrrhetic acid linked to two molecules of hexuronic acid. The method of determination involved dissolving the succ. liq. in a 50 per cent. dioxane-water mixture and then hydrolysis by refluxing with dilute sulphuric acid. Upon cooling, a precipitate of glycyrrhetic acid forms and most of it is dissolved by refluxing with chloroform. Subsequently the water-chloroform mixture is transferred to an extractor and extraction with chloroform continued for 1½ hours. After cooling, the chloroform layer is made up to a definite volume, an aliquot portion taken and evaporated to dryness and the residue dissolved in ethanol. This solution is then examined polarographically, the determination being made on 40 per cent. ethanol containing 0·1M acetate buffer [voltage range used was −1·2 to −1·7 V. (vs. S.C.E.)]. A. H. B.

Phenobarbitone and Diphenylhydantoin, Chromatography of. A. S. Curry. (*Analyst*, 1955, **80**, 902.) By the use of paper chromatography both phenobarbitone and diphenylhydantoin can be separated and a visual comparison made. The solvent system used was *n*-butanol, water, ammonia, sp.gr. 0·880 (100:66:33) with Whatman No. 1 paper; phenobarbitone had an R_F value of 0·50 and diphenylhydantoin R_F 0·65. The top layer of the solvent is used, the bottom layer being discarded. Two methods were used for the detection of the spots, the first being to contact print the dried chromatogram on Ilford Reflex Paper No. 50, using as the source, unfiltered light from a mercury-vapour lamp; after exposing to ammonia 10 to 20 μg. was visible as a white spot on a black background. In the second method the paper was dipped in a solution of 5 per cent. of mercuric oxide in 20 per cent. sulphuric acid followed by washing with water, acetone and ethanol; after dipping in 0·05 per cent. diphenylthiocarbazone in ethanol, reddish purple spots appeared after 1 to 2 minutes. Barbiturates with an allyl group in the molecule develop distinctly more blue than the fully saturated compounds, allobarbitone giving a blue spot and quinalbarbitone blue-purple. With this treatment 20 μg. phenobarbitone or 40 μg. diphenylhydantoin can be easily detected. R. E. S.

Reserpine, Fluorimetric Assay of. E. B. Dechene. (*J. Amer. pharm. Ass., Sci. Ed.*, 1955, **44**, 657.) Solutions of reserpine in 5N acetic acid were treated with 1 ml. of solution of hydrogen peroxide (3 per cent.) to increase the intensity of the fluorescence due to reserpine, and diluted to 10 ml. with 5N acetic acid. The solutions were heated for 45 minutes in a boiling water bath, cooled and the fluorescence measured by means of a photoelectric fluorimeter. The fluorescence was compared with that of a solution of reserpine of known strength, similarly treated, and the reserpine content of the test solution calculated. The intensity of fluorescence was proportional to concentration of reserpine in the range of 0·4–1·8 μg. This method was applied to the determination of reserpine in tablets, and was also used in the assay of a powdered extract of *Rauwolfia serpentina*. In the latter case, preliminary treatment involving extraction with methanol, evaporation, maceration of the residue with N sulphuric acid, extraction with chloroform, washing with sodium bicarbonate solution, evaporation and solution in acetic acid was necessary. G. B.

Vitamins D, Colour Reaction for. W. I. Lyness and F. W. Quackenbush. (*Analyt. Chem.*, 1955, **27**, 1978.) Calciferol and vitamin D_3 were found to react with an iodine-ethylene dichloride reagent to produce a strong yellow colour which showed an absorption maximum at 450 mμ. The intensity of the colour was enhanced by mercuric *p*-chlorobenzoate and certain other compounds. Six sterols, lumisterol, ergosterol, 7-dehydrocholesterol, cholesterol, stigmasterol, and sitosterol, when tested at 0·05 and 0·5 mM concentrations showed no apparent reaction with the reagent. Vitamin A (0·20 mM solution) produced a medium blue colour which changed after approximately 1 minute to medium violet, the solution showing a broad absorption band with a maximum at 555 mμ and some absorption at 450 mμ; vitamin A interfered with the determination of vitamin D to give low values. When the mercuric *p*-chlorobenzoate was omitted from the reagent, colour development was qualitatively the same but quantitatively about 10 to 15 per cent. of the intensity. Temperature differences between 20° and 35° C., were shown to have no effect on the reaction. A precision within 2 per cent. was obtained under strictly controlled conditions. R. E. S.

BIOCHEMISTRY

GENERAL BIOCHEMISTRY

The Antivitamin B_{12} Activity of Some Compounds Related to Cobalamin. W. F. J. Cuthbertson, J. Gregory, P. O'Sullivan and H. F. Pegler. (*Biochem. J.*, 1956, **62**, 15P.) A cup-plate method has been devised for detecting compounds that antagonise the utilisation of cyanocobalamin by vitamin B_{12}-dependent organisms. Solutions of cyanocobalamin (0·1 μg./ml.) and the test substance (1–1000 μg./ml.) were placed in cups cut 8 mm. apart in vitamin B_{12} assay plates seeded with either *Escherichia coli* or *Lactobacillus leichmannii*, and the plates incubated overnight. Inert substances did not modify the circular zones of growth; non-specific inhibitors, such as phenol, produced circular zones of inhibition, cutting arcs from the growth produced by the vitamin in the adjacent cup. Competitive antagonists showed inhibition which decreased rapidly towards the centre of the growth zone and extended further round the edges than with non-specific growth inhibitors. Quantitative assessment was carried out in fluid media using graded levels of vitamin B_{12} and antagonist. The methylamide of the mixed monobasic acids derived from cobalamin was the most active of the substances tested. Vitamin B_{12}-deficient rats were fed mixtures of the vitamin and antagonist at varying dose levels and the antagonists depressed growth at doses of 0·1–3 μg./day. J. B. S.

Vitamin B_{12}, Antimetabolites from. E. Lester Smith, L. F. J. Parker and D. E. Gant. (*Biochem. J.*, 1956, **62**, 14P.) The mono-, di- and tricarboxylic acids resulting from the mild hydrolysis of vitamin B_{12} have been reacted in anhydrous dimethylformamide solution, first with ethyl chloroformate and triethylamine, and then with amines (instead of ammonia as used in the regeneration of the vitamin) to yield amides, which have been examined for anti-vitamin activity. The products were purified by electrophoresis on paper, and by repeated paper chromatography. Antivitamin activity was demonstrated by plate assay with the B_{12}-requiring *Escherichia coli* mutant for the mono-amides of methylamine, ethylamine, monoethanolamine, ethylenediamine, dimethylamine, diethylamine, piperidine, phenylethylamine, *cyclo*hexylamine, aniline and sulphanilic acid. The di-anilides of the dibasic acids were inactive, whilst the tribasic acid gave a weekly active triethylamide.

J. B. S.

BIOCHEMICAL ANALYSIS

5-Hydroxyindoleacetic Acid in Urine, Determination of. A. Hanson and F. Serin. (*Lancet*, 1955, **269**, 1359.) A qualitative and a quantitative method are described for the determination of 5-hydroxyindoleacetic acid, the main excretory metabolite of 5-hydroxytryptamine, in urine. As a screen test, make 100 ml. of the 24 hour urine specimen alkaline to pH 8·5 with ammonia, filter and extract twice with ether to remove impurities. Acidify to pH 4 with dilute hydrochloric acid, filter and extract three times with 100 ml. of ether. Dehydrate the pooled ether extracts with anhydrous sodium sulphate, evaporate to dryness *in vacuo* and dissolve the residue in ethanol. Paper chromatography is used for identification, using a solvent mixture of *n*-butanol acetic acid water (4:1:5) and the spots are developed by spraying with an ethanolic solution of *p*-dimethylaminobenzaldehyde or a solution of 2-nitrobenzenediazonium-naphthalenesulphonate in dilute hydrochloric acid. For quantitative determina-

tion acidify 2 ml. of filtered urine with one or two drops of 10 per cent. hydrochloric acid and extract twice with 25 ml. of ether. Filter the pooled ether extracts, dehydrate and evaporate to dryness at 50° C. Dissolve the residue in 0·1N hydrochloric acid and to 2 ml. of this add 5 ml. of Ehrlich's aldehyde reagent. Heat the solution and a blank for 2 hours at 45–50° C., when the solution becomes blue. Dilute with cold 50 per cent. ethanol to 10 ml. and measure the colour in a spectrophotometer at 590 mμ. The urinary excretion has been studied in two patients with malignant carcinoid. G. F. S.

Urea in Blood and Urine, Determination of. H. L. Rosenthal. (*Analyt. Chem.*, 1955, **27**, 1980.) The Fearon condensation of urea with acidified diacetyl monoxime followed by oxidation with arsenic acid has been extensively studied in an effort to improve reproducibility and the linearity of response of the reaction. The concentration of mineral acid and oxidising arsenic was found to be critical; in 3·8N hydrochloric acid and 0·08N arsenic acid maximum colour is produced which conforms to Beer's law at urea concentrations up to 60 μg. per 10-ml. reaction volume. Dilution of the reaction mixture results in deviation from Beer's law, and the urea response curve no longer passes through the origin. The colour formation increased rapidly on heating in a boiling water bath, being 90 per cent. complete in 25 minutes; a 30 minute heating period was found to give the most reproducible results. Recovery experiments, with known amounts of urea added to blood and urine, gave individual recoveries ranging from 94 to 103 per cent. in blood and 92 to 110 per cent. in urine. Although the reaction is not specific for urea, only this substance gives a yellow colour with absorption maximum at 480 to 485 mμ.; for example, citrulline and other carbamyl amino-acids give maximum absorption at 550 mμ.

R. E. S.

CHEMOTHERAPY

Phenoxymethylpenicillin. W. J. Martin, D. R. Nichols and F. R. Heilman. (*Proc. Mayo Clin.*, 1955, **30**, 467.) Phenoxymethylpenicillin (penicillin V) is produced biosynthetically by *Penicillium chrysogenum* Q 176 in a culture medium containing a special type of nutrient substrate. It is an acid and therefore passes through the stomach unchanged, in contrast to benzylpenicillin which is partly inactivated in an acid medium. In the alkaline medium of the small intestine it dissolves and is absorbed. It is stable as a free acid and does not require to be prepared as a metallic or organic salt. Phenoxymethylpenicillin is readily absorbed into the serum when administered by the oral route. Administration of 200,000 units every 4 hours produces serum levels effective in combating minor infections due to susceptible organisms; for infections of moderate severity a dose of 400,000 units 4-hourly appears adequate, and 800,000 units has been given for fairly severe infections. The range of antibacterial activity appears to be similar to that of benzylpenicillin. Encouraging results were obtained from the use of phenoxymethylpenicillin in the treatment of 30 patients suffering from a wide variety of infections. The most frequently encountered side effect was a mild gastro-intestinal irritation manifested by slight abdominal cramping and diarrhœa. One patient experienced rather severe aphthous stomatitis. It appears that many of the infections that have been treated parenterally with penicillin in the past may now be treated with phenoxymethylpenicillin given orally. S. L. W.

Streptonivicin (Albamycin). W. J. Martin, F. R. Heilman, D. R. Nichols, W. E. Wellman and J. E. Geraci. (*Proc. Mayo Clin.*, 1955, **30**, 540.) Streptonivicin is an antibiotic produced by an actinomycete, *Streptomyces niveus*. It is relatively stable and is active against a variety of organisms; it is especially active, both *in vitro* and *in vivo*, against *Micrococcus pyogenes*. There is apparently no cross-resistance between streptonivicin and penicillin, streptomycin, chloramphenicol, the tetracycline group of compounds, neomycin, bacitracin, and erythromycin, and organisms resistant to them may be fully susceptible to streptonivicin. Laboratory evidence indicates that *M. pyogenes* can become resistant to streptonivicin. Administration of multiple doses of streptonivicin, 0·25 to 0·5 g., at intervals of 6 hours to a number of patients, showed that it is absorbed into the general circulation when given by this route; detectable levels persist in the serum for more than 12 hours after administration. The drug is distributed in blood, pleural and ascitic fluids, and thyroid tissue, and is excreted in the bile, urine and fæces. The kidneys are one of the main routes of excretion. There are indications that the antibiotic in the urine is changed but that it is biologically active. The drug was not detected in the cerebrospinal fluid. Streptonivicin appears to be relatively non-toxic in the doses used in this study, and none of the patients receiving it suffered damage to the kidneys, liver or hæmopoietic system. Some of the patients complained of nausea. If these experimental data are substantiated clinically, streptonivicin may prove effective in the treatment of infections caused by strains of *M. pyogenes* which are resistant to other antibiotics. S. L. W.

PHARMACY

NOTES AND FORMULÆ

Antacids, Comparative Evaluation by Various Methods. R. E. Booth and J. K. Dale. (*J. Amer. pharm. Ass., Sci. Ed.*, 1955, **44**, 694.) Three antacid preparations were tested by 9 methods described in the literature and the results compared. Varying amounts of acid solution, sometimes containing pepsin, were used, the pH being determined at intervals. In some of the methods a quantity of solution was discarded at intervals and more acid added. In each case curves of pH against time were drawn, and considerable differences were observed when the same antacid was tested by different methods. In general, the pH increased more rapidly when the rate of stirring was increased. Increasing the working temperature had very little effect when testing rapid-acting products, such as a mixture of magnesium carbonate, magnesium trisilicate and calcium carbonate or a mixture of magnesium carbonate, magnesium oxide and calcium carbonate, but a much lower pH was reached at the higher temperatures with a preparation containing dried aluminium hydroxide gel and magnesium trisilicate. It was necessary to repeat the experiments several times in order to produce reliable curves. G. B.

Aneurine Hydrochloride, Effect of, on the Stability of Solutions of Crystalline Vitamin B_{12}. B. A. Feller and T. J. Macek. (*J. Amer. pharm. Ass. Sci., Ed.*, 1955, **44**, 662.) Solutions of reaction pH 4 containing vitamin B_{12} with 10 mg./ml. of aneurine hydrochloride were found to be stable at room temperature, but decomposition occurred rapidly on autoclaving, 62 per cent. of the vitamin B_{12} being decomposed in 60 minutes at 120° C. Experiments with solutions containing aneurine hydrochloride and its decomposition products, 2-methyl-4-amino-5-hydroxymethylpyrimidine and 4-methyl-5-β-hydroxyethylthiazole

showed that the decomposition was caused by the thiazole part of the aneurine molecule. Solutions of vitamin B_{12} alone were not decomposed by autoclaving at 120° C. G. B.

Turbidity, Limit Test for. K. Ilver, A. Jackerott and F. Reimers. (*Dansk. Tidsskr. Farm.*, 1955, **29**, 153.) Solutions of commercial chemical products may give turbid solutions owing to the presence of impurities and a limit test is desirable. Kaolin suspensions are not suitable for use as turbidity standards because of the variation between different samples of kaolin and because the particles are coarser than those usually encountered as impurities in commercial chemicals. Barium sulphate suspensions having a suitable particle size may be prepared as follows. Place at the bottom of a test-tube 1 ml. of solution of barium chloride containing 0·5 mg. of barium per ml. in ethanol (85 per cent. w/w) and add 1 ml. of M sulphuric acid, blowing it out from the pipette and shaking all the time. After 5 minutes add 10 ml. of water and mix. The suspension should be used as a standard of comparison within 20 minutes of its preparation. The presence of ethanol improves the reproducibility of the standard. In carrying out the limit test for turbidity, a solution of the sample under test is compared with the standard turbidity in daylight in clear colourless test-tubes observed horizontally in direct daylight against a black background. G. B.

PHARMACOLOGY AND THERAPEUTICS

Acetazoleamide, a Carbonic Anhydrase Inhibitor, Mechanism of the Anticonvulsant Action of. J. G. Millichap, D. M. Woodbury and L. S. Goodman. (*J. Pharmacol.*, 1955, **115**, 251.) The relationship between the anticonvulsant action of acetazoleamide and sulphanilamide and their inhibition of carbonic anhydrase was investigated in mice after oral administration. The time of maximum effect and the relative anticonvulsant potencies of the drugs were determined by the maximal electroshock seizure test. Brain inhibitor concentrations were measured both indirectly, from the degree of inhibition of brain carbonic anhydrase, and directly, by chemical and bioassay techniques. The anticonvulsant ED50 of sulphanilamide was 140 mg./kg. and of acetazoleamide 74 mg./kg., both doses inhibiting the brain enzyme by about 98 per cent. The anticonvulsant activity of the drugs was independent of the secondary metabolic acidosis caused by inhibition of kidney carbonic anhydrase. The time of peak anticonvulsant activity of acetazoleamide (3 hours) and of sulphanilamide (1½ hours) corresponded with their times of maximal inhibition of brain carbonic anhydrase. *In vitro* at 0° C., acetazoleamide was 100 times more active in inhibiting mouse erythrocyte carbonic anhydrase than was sulphanilamide. Anticonvulsant and brain-enzyme inhibiting potencies of the two drugs are reconcilable with the *in vitro* results, for at the same dose level, the ratio of brain localisation of acetazoleamide compared with sulphanilamide was 1 : 50. Phenobarbitone, trimethadione and diphenylhydantoin, in anticonvulsant doses, did not inhibit brain carbonic anhydrase. In the sulphonamides, a free $-SO_2NH_2$ group was found to be necessary for both anticonvulsant activity and inhibition of carbonic anhydrase; sulphathiazole had neither activity. CO_2 accumulation may be of significance in prevention of seizures by acetazoleamide; also, preliminary experiments show a decrease in total brain sodium and an increased brain intracellular/extracellular potassium ratio. G. P.

Analgesics and Nalorphine, Action of, on the Cough Reflex. A. F. Green and N. B. Ward. (*Brit. J. Pharmacol.*, 1955, **10**, 418.) Some morphine-like

analgesics were compared for antitussive activity on the cough reflex induced in lightly anæsthetised cats by electrical stimulation of the superior laryngeal nerve. This method did not induce the reflex in dogs, so with these animals and with guinea-pigs, coughing was caused by simple mechanical irritation of the tracheal mucosa or by a chemical method (introduction of SO_2 into the tracheal cannula). The suppression of the cough reflex did not appear to depend on the type of stimulus, nor was there any great species difference in the actions of the drugs. The order of antitussive activity of the analgesics, taking methadone, the most potent, as unity, were:—piperidyl amidone 1/2; thiambutene 1/4; morphine 1/8; pethidine 1/20; pholcodine 1/40; and codeine 1/80. The activity of narcotine was negligible. These values for potency are of the same relative order of magnitude as those already known to cause other morphine-like effects. In relation to its antitussive effect morphine depressed respiration most, and pethidine least, in the cat. Nalorphine readily antagonised the antitussive action of the analgesics, as did *N*-propylnormorphine with codeine, but nalorphine had no effect on the cough depressant actions of pholcodine or narcotine. G. P.

Antrycide, Action upon Trypanosomes *In Vitro*. F. Hawking and J. P. Thurston. (*Brit. J. Pharmacol.*, 1955, **10**, 454.) The minimal *in vitro* trypanocidal concentration of antrycide methylsulphate against *Trypanosoma equiperdum*, was 10^{-6} to $2{\cdot}5 \times 10^{-7}$. The trypanosomes were incubated at 35° C. for 20 hours with a horse serum—Tyrode mixture containing the drug. For an antrycide-resistant strain the minimal effective concentration under the same conditions was only four times greater; this resistant strain was unaffected by maximum tolerated doses *in vivo*. The power of normal trypanosomes to infect mice was destroyed by *in vitro* exposure to antrycide 10^{-6} for 5 hours at 35° C., whereas antrycide-resistant trypanosomes still retained high infective power after similar exposure to a concentration of 4×10^{-6}. This property of antrycide to abolish the infectivity is probably more important for its therapeutic action *in vivo* than is its direct trypanocidal action *in vitro*. Similar loss of infectivity is seen with suramin and phenanthridinium compounds. A possible explanation is that these compounds suppress the multiplication of the trypanosomes. G. P.

Benactyzine, General Pharmacology of. V. Larsen. (*Acta pharm. tox., Kbh.*, 1955, **11**, 405.) Benactyzine (benzilic acid diethylaminoethylester hydrochloride, Suavitil) was first synthesised during a systematic search for compounds with atropine-like activity. It has a low, both acute and chronic, toxicity when given to miec, rats, guinea-pigs, rabbits and cats. It reduces the barium-induced spasm and it also has an antiacetylcholine effect when tested on the isolated intestine of the guinea-pig and on the heart and the blood pressure of the rabbit. An anticholinergic effect on salivary secretion and on the movements of the stomach *in situ* after vagal stimulation can be demonstrated. It has strong local anæsthetic properties. It does not lower the body temperature in rabbits and it has neither adrenergic blocking nor ganglion blocking actions. In man benactyzine has a peculiar and rather specific effect on a series of higher functions of the brain, leading to some blocking of the thoughts, a certain insusceptibility to unpleasant mental impressions and decreased power of decision. It has no hypnotic effect *per se*, although it produces some drowsiness and dizziness and a feeling of considerable relaxation in the limb muscles. M. M.

Cardiac Glycosides, and Other Compounds, Effects of, on Cation Transfer in Human Erythrocytes. J. B. Kahn and G. H. Acheson. (*J. Pharmacol.* 1955, **115**, 305.) The influence of drugs on the cation exchange of human erythrocytes was studied employing standard techniques for separation of cells and plasma. Cation flux in fresh cells under steady state conditions was studied using radioactive potassium, ^{42}K. Concentration of cations was measured photometrically. Most values are recorded as plasma potassium (K_p) concentration and cellular sodium (Na_c) concentration, representing a shift of compartment of Na or K, with whole-blood values remaining constant. On cold storage, K_p concentration increased whilst Na_c concentration increased to a greater extent, giving a net gain of intracellular cation. Incubation at 37° C. reversed these changes, the cells gaining K and losing Na. In incubated cold-stored cells, the net influx of K was greater than the total influx of ^{42}K in fresh blood. Ouabain, strophanthidin, 3-acetyl strophanthidin, digitoxin, and desacetyl lanatoside-C, in suitable concentrations, completely inhibited the active phase of cation transport, and the flux of cations was slightly reversed. These changes were attributed to a block of the metabolic phase of cation transport. There were up to 30-fold differences of potency among the glycosides and genins tested, which did not result from differences in plasma binding as tested with ouabain and digitoxin. In glycoside-treated fresh blood, the rate of net efflux of K_c corresponded closely with the total efflux of K in equilibrium conditions (as deduced from the influx of ^{42}K) and remained roughly constant at one, two and four hours of incubation, despite a rise of K_p and a fall of K_c. Net efflux of K did not correlate with either K_p concentration, or the concentration gradient (K_c–K_p), but there was close correspondence with K_c concentration. Angelicalactone, butyrolactone and propiolactone, in a concentration one million times greater than ouabain, also inhibited cation transport. Other drugs tried, but which were without detectable effect in the concentration used (10^{-4} to 10^{-5}) included several pure veratrum alkaloids, andromedotoxin, adrenaline, tetraethylammonium, tubocurarine, 2:4-dinitrophenol and acetazoleamide. The presence of a lactone ring in a molecule does not necessarily confer activity in blocking cation transport. In active lactones, potency is enhanced by a *cyclo*pentanophenanthrene ring, the degree of increase possibly being related to the number and position of –OH groups on the steroid moiety, and the position of the double bond in the unsaturated lactones. G. P.

Chlorpromazine Hydrochloride, Side Effects of. E. M. Glaser and P. S. B. Newling. (*Brit. J. Pharmacol.*, 1955, **10**, 429.) The incidence of side effects of chlorpromazine, in single doses of 25 and 50 mg., was compared in normal healthy subjects with those of 0·75 mg. hyoscine hydrobromide and a lactose placebo. Each drug was given orally in tablet form, neither subjects nor experimenters knowing the identity of the tablets until completion of the tests. The 25 mg. dose of chlorpromazine had little effect, but with 50 mg. the effects produced were similar to those of the hyoscine, particularly sleepiness, tiredness and dryness of the mouth. However, 50 mg. chlorpromazine increased the heart rate, while the hyoscine reduced it. When subjects, previously given the placebo, hyoscine or the 25 mg. dose of chlorpromazine, received further similar doses of the same drugs, the frequency of symptoms reported after the fifth successive daily dose was significantly different from that obtained with the first dose (i.e., habituation to the experimental procedure had taken place). This did not occur with the 50 mg. dose of chlorpromazine, there being no significant difference between first and fifth doses; this suggests that this dose of chlorpromazine was inhibiting the induction of habituation, probably by depression of the cerebral cortex. G. P.

α-Cocaine. R. Foster, H. R. Ing and V. Varagić. (*Brit. J. Pharmacol.*, 1955, **10**, 436.) Contrary to the accepted statement by Willstatter that α-cocaine was without local anæsthetic activity, tests by the guinea-pig intradermal weal method and by application to the lumbar nerve plexus of frogs show it to be one-fifth as active as cocaine by the first method and three-fifths as active by the second. α-Cocaine inhibited, to the same degree, amine oxidase preparations from homogenates of cat and rabbit liver, of the nictitating membrane of the cat and of rabbit's uterus. However, on the isolated uterus, duodenum and ear preparations of the rabbit, α-cocaine either reduced the effects of adrenaline or had no effect. Cocaine, on the other hand, always potentiated the actions of adrenaline and noradrenaline on the uterus and perfused ear. There was occasional potentiation, by α-cocaine, of the action of adrenaline on the isolated auricles of the rabbit, but this was always less than that produced by cocaine. In the spinal cat, α-cocaine had no effect on the pressor action or contraction of the nictitating membrane caused by adrenaline and noradrenaline, although the doses of α-cocaine used were five times larger than doses of cocaine having a marked potentiating effect on the actions of the catechol amines. These results indicate that the suggestion by Burn and Robinson (*Brit. J. Pharmacol.*, 1952, **7**, 304), that cocaine potentiates adrenaline and noradrenaline through inhibition of amine oxidase, is incorrect. G. P.

Compound 48/80, Effect of, on Mammalian Skeletal Muscle. G. Sömjén and I. E. Uyldert. (*Brit. J. Pharmacol.*, 1955, **10**, 413.) The histamine liberator, compound 48/80, blocked neuromuscular transmission *in vivo* in the rat and rabbit, and in the isolated rat diaphragm—phrenic nerve preparation. The response of the muscles to direct stimulation was not affected. In some ways the block resembled that of (+)-tubocurarine in that a tetanus was not maintained during partial block and there was some post-tetanic reversal of the block; also, a dose of (+)-tubocurarine given between two 48/80 injections potentiated the effects of the second injection. In addition, 48/80 caused no contraction or contracture of the chronically denervated gastrocnemius muscle of the rat. However, neuromuscular paralysis, complete or partial, was not antagonised by anticholinesterases. Paralysis was apparently due to an action of the drug itself and not through histamine release, since there was no tachyphylaxis; nor did histamine reproduce the paralysis, or mepyramine antagonise it. G. P.

Cycloserine in Urinary Infections. R. D. Herrold, A. V. Boand and M. Kamp. (*Antibiotic Med.*, 1956, **1**, 665.) This report is based on clinical and bacteriological observations of 124 patients given cycloserine during a period of 8 months. All the patients were refractory cases who had failed to respond to intensive treatment with other antibiotics. Three groups of patients were studied, those with bladder or bladder and upper urinary tract infections, those with lower urinary tract infections (except gonococcic), and those with gonococcic infections. Among the 49 patients in the first group the predominant organisms were *Escherichia coli*, 17; *Proteus*, 14; followed by *Aerobacter aerogenes*, *Pseudomonas*, *Paracolon* and 2 instances each of staphylococci and streptococci; many were mixed infections. Of the 49 patients, there were 24 cures, 20 failures and 5 with insufficient follow-up. The group of 19 patients with lower urinary tract infections included cases of prostatitis with or without symptomatic urethritis; 12 had gram-positive flora, while 7 had some type of gram-negative bacilli usually mixed with gram-positive organisms. In this group there were 10 cures, in 3 of which cycloserine was

given concurrently with streptomycin, 5 failures, and 4 with insufficient follow-up. The third group consisted of 56 gonococcic infections, all in male patients. There was almost no improvement, clinically or bacteriologically, in any of these patients. The side reactions with cycloserine were few and consisted chiefly of vertigo, drowsiness, light headedness and ocular disturbance; there were occasional complaints of nausea, but no other gastro-intestinal disturbances. Children tolerated the drug well, the poorest tolerance being in elderly patients. The optimum dose is 1 g. daily by mouth in divided doses. The action appears to be bacteriostatic and often, in the more chronic infections, a favourable response is not evident in less than 10 to 14 days of medication, which would appear to be the minimum period of administration. In general, resistance to cycloserine does not seem to develop quickly. In several instances there seemed to be an advantage in combining cycloserine with streptomycin. S. L. W.

Dextran-Iron Complex in Hypochromic Anæmia. A. Grunberg and J. L. Blair. (*Arch. intern. Med.*, 1955, **96**, 731.) A dextran-iron preparation (containing 50 mg./ml. of iron) suitable for intramuscular use was given to 30 patients suffering from hypochromic anæmia. The response was satisfactory and was indistinguishable from that obtained with intravenous iron therapy. The total amount of iron administered was given in divided doses commencing with two injections of 100 mg. each and continuing with 250 mg. on subsequent occasions; injections were given on alternate days. Injections were given into the upper third of the outer side of the thigh. Apart from slight transient brownish discolouration at the site of injection in a few cases there were no local reactions. None of the patients showed any constitutional disturbance and all claimed to feel definitely better within 7 to 10 days of commencing treatment. By the time the final injection was given there was in all cases a significant increase in the hæmoglobin level. Details are given of 5 cases. S. L. W.

2-Diethanolamino-5-nitropyridine, Amœbicidal Action of. R. A. Neal and P. Vincent. (*Brit. J. Pharmacol.*, 1955, **10**, 434.) The amoebicidal activity of 2-diethanolamino-5-nitropyridine (263C49), was equal to that of chiniofon on rats experimentally infected with an invasive strain of *Entamœba histolytica*. With non-invasive strains of *E. histolytica* chiniofon was more effective, and 263C49 less effective, than on the invasive strains. 263C49 had no effect on experimentally-induced amœbic liver abcesses in the hamster. Toxicity of 263C49 was low and the drug was rapidly excreted in the urine. *In vitro* the new drug had a direct action, in the same minimal concentrations as chiniofon, on amœbæ grown on a horse serum—eggwhite medium; on one strain 263C49 was ten times more active than chinifon. In a small clinical trial with large doses of 263C49 (51 g. given orally over ten days) all cases were rapidly cleared of symptoms, but a proportion showed parasitological relapse after termination of treatment. G. P.

Glutethimide (Doriden), Clinical Trial of. M. Rushbrooke, E. S. B. Wilson, J. D. Acland and G. M. Wilson. (*Brit. med. J.*, 1956, **1**, 139.) Glutethimide (α-phenyl-α-ethyl-glutarimide), a new hypnotic, was investigated in a general practice, using ranking methods, and its effect compared with that of cyclobarbitone and an inert tablet. The trials were conducted on 18 patients, all of whom had previously been taking a barbiturate. Glutethimide 0·5 g., cyclobarbitone 0·2 g., and inert tablets were prepared so that they were identical in appearance, and all contained 3·6 mg. of quinine sulphate so that the taste was similar and the barbiturate could not be distinguished. In the dosage used glutethimide was found to

compare favourably with cyclobarbitone. Fourteen of the patients put the placebo in the third phase of preference, 10 chose glutethimide for first place and 6 cyclobarbitone. The estimates of the times in getting to sleep after each treatment were: glutethimide 71 ± 8·5 minutes; cyclobarbitone 84 ± 10·7 minutes; placebo, 138 ± 20·8 minutes. It was impossible to make any satisfactory analysis of the duration of sleep. Drowsiness on the following morning was noticed on 7 occasions after cyclobarbitone and on 4 occasions after glutethimide. After completion of this trial glutethimide was given as a hypnotic to 30 patients, either in hospital or general practice. The length of the courses varied from 3 to 80 days and the dose was 0·25 or 0·5 g. at night. No definite evidence of habituation or tolerance was obtained. In two patients a skin rash developed, but disappeared within 2 days after discontinuing the drug. In one patient mental confusion and excitement developed 1½ hours after giving 0·5 glutethimide and persisted for 3 hours; a second dose was given 4 days later with a similar result. Some statistical considerations in the use of ranking methods are appended to this paper. S. L. W.

Heparin, Function of. J. F. Riley, D. M. Shepherd, G. B. West and S. W. Stroud, (*Nature, Lond.*, 1955, **176**, 1123.) Both heparin and histamine are concentrated in tissue mast cells. In the dog release of histamine, caused by damage to the mast cells by peptone or by compound 48/80, is accompanied by the realease of heparin and a consequent increase in the clotting time of blood. This dual effect has been found only in the dog. To determine what happens in the rat following a maximal release of histamine the animals were given doses of 48/80 over a period of 5 days. At the end of this time there was widespread degranulation and disruption of the mast cells in the subcutaneous tissue. 94 per cent. of the histamine but only 53 per cent. of the tissue heparin was lost. This loss of heparin was unaccompanied by any sign of the release of the heparin into the circulating blood, since the clotting time remained normal.

Thus the almost complete release of histamine from the subcutis of the rat by compound 48/80 is accompanied by a loss of only half the associated heparin. Some of the metachromatic material from the disrupted mast cells may be disposed of locally by macrophages, some may adhere to adjacent connective tissue fibrils or cells, while some may be bound by the basic histamine-liberator itself. Although these same basic compounds can release active heparin into the blood stream of the dog, they fail to do so in the rat. The rabbit and the guinea-pig are similar to the rat. This suggests that the function of heparin may be concerned rather with events in the tissues than with the coagulability of the circulating blood. M. M.

Heparin Preparations, Assay of. J. E. Jorpes. (*Acta pharm. tox., Kbh.*, 1955, **11**, 367.) Experience of different methods for the determination of the anticoagulant activity of heparin preparations is summarised. Because the effects of heparin in the blood are both on thromboplastin formation in plasma and on thrombin action, fresh whole blood is considered to be the best medium for determining the relative strength of heparin preparations. Some drawbacks of the thrombin methods and the methods with recalcified oxalated or citrated plasma, or other artificial coagulation systems, are demonstrated. Details of an *in vivo* method are given, in which the heparin is injected intravenously into sheep and the subsequent coagulation time of the blood determined. Such a method gave results in good agreement with the fresh whole blood technique. For the assay of heparin samples to be used clinically, preference is given to the methods using fresh whole blood. M. M.

21-Hydroxypregnanedione Sodium Succinate, Pharmacological Properties of. S. Y. P'an, J. F. Gardocki, D. E. Hutcheon, H. Rudel, M. J. Kodet and G. D. Laubach (*J. Pharmacol.*, 1955, **115**, 432.) Hydroxydione, (21-hydroxypregnanedione sodium succinate, Viadril or P-55) a water-soluble steroid had pronounced central nervous system depressant activity in mice, rats, rabbits, dogs and monkeys. It produced surgical anæsthesia after either oral or intravenous administration. Onset of anæsthesia was smooth, without pre-anæsthetic excitement and recovery was rapid. Duration of anæsthesia varied with the dose given. With hydroxydione there was less cardiac or respiratory depression than with thiopentone sodium. Acute toxicity was low so that therapeutic indices after intravenous administration (11·6 in mice, 7·8 in rats and 6·3 in rabbits) were considerably greater than those of thiopentone sodium. There was no evidence or androgenic, œstrogenic, progestational, corticoid or gonadotrophic activity with the steroid. Also there was no sex specificity in anæsthetic activity of toxicity, as has been found in other cases of steroid anæsthesia. Liver damage or nephrectomy did not affect either intensity or duration of anæsthesia with hydroxydione. Preliminary results in over 100 human operations confirm the superiority of the steroid over the thiobarbiturates in clinical applications in basal or general anæsthesia. G. P.

Levallorphan Tartrate, Effects on Respiration of Rabbits given Morphine. J. W. Miller, T. M. Gilfoil and F. E. Shideman. (*J. Pharmacol.*, 1955, **115**, 350.) The duration and character of levallorphan antagonism of morphine-induced respiratory depression in unæsthetised male rabbits was examined. 4 mg./kg. morphine i.v. caused 50 per cent. reduction in respiratory minute volume, with only partial recovery in 6 hours. Levallorphan, 30 minutes after morphine, gave antagonism with degree and duration directly proportional to dosage employed. Antagonism by levallorphan was not maintained. 32 mg./kg. morphine had a respiratory stimulant component, the net resulting depression being less than with 4 mg./kg.; against this the antagonism of small doses (2·5 to 5·0 mg./kg.) of levallorphan was of short duration: at 2 hours the minute volume was less than that of animals not receiving the antagonist. Curves relating degree of antagonism and dose of levallorphan at 30 minutes indicate a relationship with morphine dose employed, rather than degree of respiratory depression. The levallorphan dose required to antagonise 4 mg./kg. morphine depression back to control levels, increased with time, reaching a maximum in 2 to 3 hours and declining thereafter. Respiratory rate was depressed 50 per cent., and tidal volume increased 20 per cent. in morphinised (4 mg./kg.) animals: the tidal volume was not greatly altered by levallorphan but respiratory rate increased significantly. Increased minute volume following levallorphan administration is primarily due to increased respiratory rate superimposed on pre-existing elevated tidal volume. Codeine phosphate also antagonised morphine respiratory depression. Levallorphan alone produced stimulation or depression of respiratory minute volume, depending on dosage and time after administration. Authors interpret their results on the basis of competition for receptor sites between two pharmacologically similar agents, the less potent (levallorphan) having the greater receptor affinity. The combined effect of levallorphan and morphine on respiration at any given time, is regarded as the summation of processes producing depression and stimulation; the sum in each case depending on the dose of each agent administered, balanced against its destruction, metabolism and excretion. G. P.

Mersoben, Clinical Evaluation of. R. H. Chaney and R. F. Maronde. (*Amer. J. med. Sci.*, 1956, **231**, 26.) This is a report of an investigation to determine the diuretic activity and side effects of the compound Mersoben, 3-[2-hydroxy-3(-D-gluco-pentahydroxyhexyl-mercaptomercuri)-propyl]-D-mannitol, dispensed as a lyophilised, white, amorphous, hygroscopic solid in 2 ml. ampoules, which is readily dissolved in distilled water immediately before intramuscular or subcutaneous injection. Eighty-five patients were given a single intramuscular injection of Mersoben; most of the patients were chronic cardiac cases, who had previously been receiving meralluride for many weeks. Another group of 32 patients was given injections of meralluride for comparison. The efficacy of diuretic activity was based on a loss of weight of over 3 pounds within 24 hours following injection. On this basis Mersoben was shown to be a potent diuretic comparing favourably with meralluride. A comparison of mercury levels in the organs of an additional 15 terminal patients who had received no mercury other than one injection of Mersoben with those of patients who had received meralluride showed the values of the former to be lower for all organs except the brain. Side-effects of Mersoben were minimal with the doses used, and there was no evidence of local, renal or systemic ill effects, except infrequent local pain and rare sensitivity reaction (a mild, generalised skin rash developed in 3 patients). The development of "low salt syndrome" should be guarded against with Mersoben as with other mercurial diuretics. S. L. W.

Nitrofurantoin in Urinary Tract Infections. W. A. Richards, E. Riss, E. H. Kass and M. Finland. (*Arch. intern. Med.*, 1955, **96**, 437.) Thirty-nine hospital patients with urinary tract infections were treated with nitrofurantoin in doses of 100 to 200 mg. four times daily for periods ranging from 2 to 13 days, and averaging 7 days. The patients ranged in age from 14 to 93 years. Favourable clinical results were obtained in the great majority of acute and uncomplicated infections, but in a much smaller proportion of chronic cases with underlying complicating conditions in the urinary tract. Only 1 of 17 infections with *E. coli* failed to show any improvement during treatment, whereas in 6 of 13 cases of infection with *Aerobacter aerogenes* and 6 of 9 cases with *Proteus* infection there was no improvement. Of the 12 patients in the series without recognised complication only 1 failed to show any improvement and 8 showed complete subsidence of the clinical manifestation while on treatment. No consistent effectiveness was noted in the cases of acute pyelonephritis. Toxic effects were minor and mostly consisted of nausea and vomiting that was often related to the dose used. Sensitivity reactions were not encountered. Levels of nitrofurantoin in blood and urine, as determined by antibacterial action, indicated that effective concentrations are excreted in the urine but that useful levels are not attained in the blood on oral therapy. *In vitro* studies, including growth curves, indicate that the antibacterial action of nitrofurantoin is considerably depressed at the highly alkaline pH attainable in urine or when there is an excessive concentration of organisms. These studies also confirm the primary bacteriostatic action of the drug with a bactericidal effect on more susceptible strains at higher concentrations. S. L. W.

Pentamidine in the Treatment of Moniliasis. A. Stenderup, J. Bichel and F. Kissmeyer-Nielsen. (*Lancet*, 1956, **270**, 20.) *In vitro* experiments have shown that even low concentrations of stilbamidine and pentamidine often prevent the growth of *Candida albicans*. Three cases of moniliasis in patients with chronic malignant disease were successfully treated with pentamidine administered intramuscularly in a dose of 200 mg. twelve-hourly or daily for a week or ten days. S. L. W.

Prednisone and Prednisolone in Lupus Erythematosus. A. J. Bollet, S. Segal and J. J. Bunim. (*J. Amer. med. Ass.*, 1955, **159**, 1501.) This is a study of the effects of prednisone and prednisolone therapy (no difference in potency effectiveness or side-effects was noted between the two drugs) in 10 patients with systemic lupus erythematosus followed for an average period of 4 months. Nine of the 10 patients had been receiving hormone therapy (cortisone, hydrocortisone and corticotrophin) prior to admission without satisfactory control of the disease; they were having continual symptoms or periodic exacerbations of activity of the disease. The initial suppressive daily dose of prednisone varied between 20 and 60 mg. and averaged 35 mg. Maintenance doses varied between 5 and 30 mg. per day, averaging 18 mg. Comparison of this maintenance dose with the previous maintenance dose of steroid shows that prednisone has about 4 times the potency of cortisone and a little over 3 times that of hydrocortisone in controlling the manifestations of this disease. None of the patients had a complete and sustained remission, but when the maintenance dose had been reached 8 of the patients felt that they were stronger, free of annoying minor symptoms and functionally improved in contrast to their status on previous therapy. Prednisone was shown to be capable of diminishing the fever, chills, malaise, anorexia, arthritis, rash, mucous membrane lesions, cough, pleuritic and precordial pain, chest wall tenderness, pleural and pericardial friction rubs, pulmonary rates, abdominal pain and tenderness, headache, convulsive seizures, leucopenia, elevated sedimentation rate, and C-reactive protein. Renal abnormalities were in general not improved. Oedema diminished gradually during therapy. Anæmia did not improve, and alterations in serum albumin and globulin levels were only slight. Minor undesirable side-effects were seen in all 10 patients. The authors conclude that the effectiveness and limitations of prednisone and prednisolone in the treatment of systemic lupus erythematosus parallel closely those of cortisone and corticotrophin with the exception that the new steroids do not cause sodium and water retention or potassium loss when given in moderate therapeutic dosage.

S. L. W.

Probenecid, Cinchophen and Colchicine, in Gout. S. Gjørup and H. Poulsen. (*Acta pharm. tox., Kbh.*, 1955, **11**, 343.) The purpose of this paper is to investigate whether probenecid and cinchophen act on other oxypurines besides 2:6:8-trioxypurine (uric acid) and also whether colchicine acts on 2:6-dioxypurine (xanthine) and 6-monoxypurine (hypoxanthine). The uric acid and also the hypoxanthine and xanthine concentrations in the plasma and urine were determined by an enzymatic spectrophotometric method. It was found that probenecid and cinchophen caused an increase of the uric acid excretion in gouty patients. At the same time the uric acid plasma level fell. The action of these substances was of the same order as in normal individuals. Colchicine had no influence on uric acid excretion or on the level of uric acid in the plasma. The excretion and plasma levels of hypoxanthine-xanthine remained unchanged after administration of both probenecid, cinchophen and colchicine. None of the three drugs influenced the glomerular filtration rate.

M. M.

Reserpine and Chlorpromazine, Effects of, on Gastric Secretion. B. J. Haverback, T. D. Stevenson, A. Sjoerdsma and L. L. Terry. (*Amer. J. med. Sci.*, 1955, **230**, 601.) Studies in patients have shown that reserpine given orally and intravenously increases the volume and acidity of gastric secretion in man. There is also evidence that reserpine stimulates the motor function of the gastro-intestinal tract. Chlorpromazine given intramuscularly reduced

the volume of gastric secretion but did not change the free acidity—results similar to those following the administration of atropine. It is suggested that chlorpromazine is the tranquillising agent of choice when stimulation of gastric secretion is contraindicated. G. F. S.

***NNNN'*-Tetraethyl-*N'N'*-dimethyl-3-oxapentane-1 : 5-diammonium Di-monohydrogen Tartrate, a new Ganglionic Blocking Agent, Pharmacology of.** J. Fakstorp, E. Poulsen, W. Richter and M. Schilling. (*Acta pharm. tox., Kbh.*, 1955, **11**, 319.) The acute toxicity of this bis-quaternary ammonium salt was determined by intraperitoneal injection into mice. The LD50 was found to be 183 mg./kg. Intravenous administration to rabbits of 10 times the expected therapeutic dosage, for three months, caused no pathological changes other than those associated with ganglion blocking action. The ganglion blocking action of the compound, as determined on the nictitating membrane of the cat and on the isolated ileum of the guinea-pig, was found to be somewhat greater than that of hexamethonium. It had very little anticholinergic, antihistaminic or musculotropic spasmolytic activity. In the cat and rabbit it caused a marked hypotensive effect. The blood pressure response to adrenaline was increased and the response to carotid artery occlusion was diminished. The absorption and excretion were studied by the reineckate method, after intravenous, subcutaneous and oral administration in rabbits. M. M.

BACTERIOLOGY AND CLINICAL TESTS

Bacteria-excluding Filters for Oils. K. E. Avis and L. Gershenfeld. (*J. Amer. pharm. Ass., Sci. Ed.*, 1955, **44**, 682.) Various filters were tested by passing corn oil continuously through them for 84 days using alternating vacuum and gravity filtration. The filters examined included unglazed porcelain and diatomaceous earth candles, an asbestos pad and a sintered glass filter. Certain of the candles developed a relatively high rate of flow under vacuum and a decreased carbon-dioxide-water bubbling pressure during the course of the experiment. The increase in permeability was accompanied by lowering of effectiveness of the filters in retaining micro-organisms. Prolonged contact with corn oil rendered the diatomaceous earth filter candles more fragile and unreliable for the retention of *Bacillus cereus* spores and *Serratia marescens* organisms. A Selas 015 porcelain candle also appeared to be unsuitable for the sterilisation of corn oil by filtration. G. B.

***Bacteroides*, Sensitivity of Four Species of, to Antibiotics.** L. P. Garrod. (*Brit. med. J.*, 1955, **2**, 1529.) Sensitivity tests were made using plates prepared from meat extract peptone agar with added antibiotic solution and horse blood freshly lysed with saponin. The surface of the medium was divided into 12 compartments, each of which was inoculated with a different strain of *Bacteroides*. Plates were examined after incubation anærobically with 5 per cent. of carbon dioxide for 2–5 days. The minimum inhibitory concentration of penicillin, streptomycin, oxytetracycline, erythromycin, polymixin and bacitracin was determined for a total of 55 strains of *Bacteroides*. Penicillin was active against *Bacteroides fusiformis*, *necrophorus* and *melaninogenicum*. *Bacteroides fragilis* was the species most sensitive to oxytetracycline, but was resistant to penicillin. Chloramphenicol was moderately active against all species, but less active than oxytetracycline. All species were relatively resistant to streptomycin. For the treatment of infections in which the organisms have not been isolated and tested for sensitivity, penicillin is the most suitable antibiotic, except for infections of the lower bowel. These are commonly due to *Bacteroides fragilis*, for which oxytetracycline is suitable. G. B.