ABSTRACTS OF PAPERS PUBLISHED IN OTHER JOURNALS

CHEMISTRY

ANALYTICAL

Analgesics, Separation of. G. Wagner. (*Arch. Pharm. Berl.*, 1956, **289**, 8.) Salicylic acid, salicylamide and salicyl-*iso*propylamide can be separated by paper chromatography, using paper buffered at a pH of 10 or above. Under these conditions acetylsalicylic acid is completely saponified. Separation may also be carried out by ionophoresis. In the case of salicylic acid and acetylsalicylic acid the separation is carried out at pH 4 to 5. Amidopyrine, 4-aminophenazone, 4-methyl aminophenazone and pyramidon may be separated on acid buffered paper using *n*-butanol saturated with water. Phenylbutazone, phenacetin and acetanilide may be separated from caffeine and codeine at a pH of 3 or 4. In ionophoresis, phenylbutazone wanders as an anion, while pyramidon is only transported to a slight extent to the cathode. For development of the pyrazolone derivatives Dragendorff's reagent is used, while aminophenazone may be detected after diazotisation by coupling with alkaline β-naphthol. The caffeine may be detected by an acid iodine-potassium iodide solution. G. M.

Antihistaminic Agents, Identification of. A. Osol and C. N. Sideri. (*J. Amer. pharm. Ass., Sci. Ed.*, 1955, **44**, 761.) About 25 mg. of the substance under test was dissolved in 5 ml. of sulphuric acid. The colour was observed for 2 minutes. The solution was then diluted to 20 ml. with water and observed for a further 2 minutes. Where no response was obtained the experiment was repeated using nitric acid.

Substance	Colour with sulphuric acid	Colour on dilution
Antazoline hydrochloride	Colourless	Colourless[1]
Chlorcyclizine hydrochloride	Brilliant yellow	Colourless
Chloropyrilene citrate	Dark red	Brown precipitate
Chlorpheniramine maleate	Colourless	Colourless [2]
Diphenhydramine hydrochloride	Deep orange-red	White turbidity
Doxylamine succinate	Light yellow	Colourless
Methapyrilene hydrochloride	Orange-brown	Greenish-yellow
Phenindamine tartrate	Orange-brown	Colourless
Pyrathiazine hydrochloride	Pink, then brownish	Brownish
Mepyramine maleate	Cherry red	Turbid; white or cream precipitate separates
Thenyldiamine hydrochloride	Pink, then vivid orange-red	Colourless
Thonzylamine hydrochloride	Red	Turbid; white or cream precipitate separates
Tripelennamine hydrochloride	Yellow (turbid)	Colourless (turbid)

[1] Deep red with nitric acid. [2] Colourless with nitric acid.

G. B.

Œstrogen Preparations, Analysis of. P. M. Sanders, D. Banes and J. Carol. (*J. Amer. pharm. Ass., Sci. Ed.*, 1955, **44**, 727.) Samples of equine œstrogen sulphates were hydrolysed in acid alcohol, aqueous acid and dioxan-trichloroacetic acid. Acid alcohol appeared to be the most reliable method and gave results 3 to 16 per cent. higher than those obtained by the other methods. Œstrogen sulphates were also hydrolysed by converting them to acetates with acetic anhydride in hot pyridine, followed by hydrolysis

of the acetates with sodium carbonate. Good recoveries were obtained in the assay of conjugated ketosteroids, but in the case of conjugated diols the 17-hydroxyl group appeared to be esterified to some extent and to resist conversion to the acetate, making the analytical results less reliable. G. B.

Podophyllum Resin, Quantitative Estimation of Active Substances in. H. Potěšilová. (*Československ. Farm.*, 1955, **4**, 454.) Podophyllotoxin, α- and β-pelatins (series A and B) and picropodophyllin react quantitatively with alkali to give salts which result from the opening of a lactone ring; these compounds can be estimated by determining the amount of alkali required to open the ring, or the amount of acid required to close it after it has been opened. The method can be used to estimate the total amount of lactone-containing compounds, calculated as podophyllotoxin, in podophyllum resin. A 1-g. sample of resin is extracted with 10 ml. of chloroform; the chloroform is removed from the filtered extract and the residue is dried under reduced pressure at 100° C. to constant weight. A weighed sample (0·1 g.) of the residue is dissolved in 2 ml. of ethanol and the solution is immediately titrated with 0·1N sodium hydroxide, with phenolphthalein as indicator (to neutralise organic acids and free phenol groups). The neutral mixture is refluxed for 15 minutes on a water bath with 100 ml. of 0·1N sodium hydroxide, and the cooled solution is titrated with 0·1N hydrochloric acid. A further 10 ml. of 0·1N hydrochloric acid is added and the solution is heated in the same way, cooled and titrated with 0·1N sodium hydroxide. The ring-closing titration is preferred for determinations on the resin. Tests on commercial samples show that the chloroform-soluble fraction of the resin contains 79 to 97 per cent. of "podophyllotoxin." E. H.

Papaverine and its Salts, Colorimetric Determination of. O. N. Soboleva (*Aptechnoe Delo*, 1955, **4**, No. 4, 37.) Papaverine reacts with formaldehyde to form methylene-dipapaverine (Freund and Fleischer, *Ber.*, 1915, **48**, 406), and when this is treated with bromine water and ammonia a greyish violet precipitate is formed; the precipitate dissolves in ethanol to give a violet-red or blue-violet colour. The coloured compound can be extracted from dilute ethanol by chloroform, but not by ether. None of the other opium alkaloids react in the same way. For the determination of papaverine, a solution containing 0·5 to 1·5 mg. of the hydrochloride is evaporated to dryness and the residue is stirred for 30 minutes with 2 drops of 35 per cent. formaldehyde solution and 0·2 ml. of 80 per cent. sulphuric acid. The product is transferred to a 25-ml. glass-stoppered calibrated tube, the dish being washed with 0·5-ml. quantities of water. The contents of the tube are shaken for 4 minutes with 0·5 ml. of bromine water; 5 ml. of ethanol and 1 ml. of 25 per cent. ammonia solution are added, and the volume is made up to 25 ml. The colour is measured in an absorptiometer fitted with a blue filter. The error is ±5 per cent. E. H.

Protoveratrine, Determination of. J. Levine and H. Fischbach. (*J. Amer. pharm. Ass., Sci. Ed.*, 1955, **44**, 713.) A mixture of protoveratrines A and B may be separated by partition chromatography, a column consisting of 1 g. of Celite with 1 ml. of the immobile phase (2 parts of buffer solution, pH 3·5 with 1 part of ethylene glycol) being sufficient for the separation of a mixture of approximately 1 mg. of each alkaloid. 200 ml. of benzene is passed through the column to remove protoveratrine A, followed by 150 ml. of ethylene chloride to remove protoveratrine B. Protoveratrine may be

assayed by passing a chloroform solution through a Celite column incorporating buffer solution pH 3·5 and chlorophenol red (3 : 3′-dichlorophenol sulphonphthalein). The quantity of dye removed is proportional to the quantity of alkaloid present in the solution under examination. G. B.

***Rauwolfia serpentina*, Differentiation of.** D. Banes and J. Carol. (*J. Assoc. off. agric. Chem., Wash.*, 1955, **38**, 866.) Spectrophotometric analysis of the aromatic acids obtained after hydrolysing the weak alkaloids of rauwolfia root has been employed for differentiating *Rauwolfia serpentina* from other species. Six samples of whole roots of *R. serpentina* from India were analysed for derived aromatic acids; the ultra-violet absorption spectra of the isolated acids resembled those of trimethoxycinnamic trimethoxybenzoic acid mixtures. The spectra of acids derived in the same manner from *R. heterophylla*, *R. micrantha*, *R. hirsuta*, *R. canescens*, and *R. sellowi*, either resembled the curve given by trimethoxybenzoic acid, or indicated a negligibly low concentration of acyloxy alkaloids. On the basis of these observations, spectrophotometric criteria were established for the chemical identification of ground rauwolfia roots: (1) Absorbance at 303 mμ greater than that at 288 mμ ($A_{303}/A_{288} > 1$) and absorbance ratio A_{303}/A_{273} greater than 0·8 indicate the presence of *R. serpentina* (although mixtures containing *R. serpentina* and large proportions of a species poor in acyloxy alkaloids, like *R. sellowi* or *R. micrantha*, would yield a similar spectrum): (2) Absorbance ratio $A_{303}/A_{288} < 0{\cdot}6$, and $A_{303}/A_{273} < 0{\cdot}9$ indicate a species of *Rauwolfia* other than *serpentina* with other species. In the examination of a number of commercial samples the spectrophotometric procedure yielded results which were consistent with those obtained by microscopic methods. Paper chromatography could be used on the mixed acids if desired. R. E. S.

Reserpine Preparations, Chromatographic Analysis of. D. Banes, J. Carol and J. Wolff. (*J. Amer. pharm. Ass., Sci. Ed.*, 1955, **44**, 640.) Serpentine, ajmaline, ajmalicine, reserpine, recinnamine and deserpidine may be separated from each other and identified by ascending paper chromatography, using a mobile solvent consisting of *iso*octane, benzene, formamide and *cyclo*hexane, and formamide (30 per cent.) in acetone as the immobile phase. After development, the paper is dried at 90° C. and exposed to hydrochloric acid fumes to increase subsequent fluorescence of deserpidine. The spots due to the alkaloids are examined in ultra-violet radiation, and the alkaloids identified by comparison with spots due to pure samples of known alkaloids run simultaneously with the samples under test. The authors also describe a method employing a column of diatomaceous silica (Celite 545), using citric acid and ethanol as the immobile solvent and a mixture of chloroform, *iso*-octane, water and ethanol as the eluent. By this method quantities of the order of milligrams of reserpine may be separated quantitatively, and determined by ultra-violet spectrophotometric analysis. G. B.

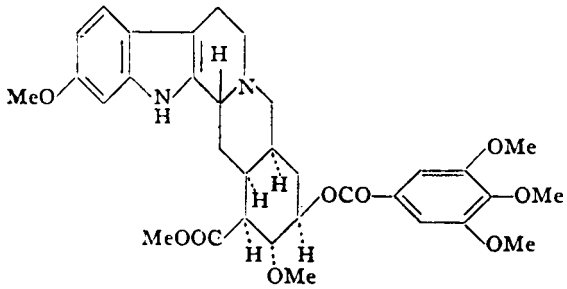
Reserpine in Pharmaceutical Products, Determination of. W. F. Bartelt and E. E. Hamlow. (*J. Amer pharm. Ass., Sci. Ed.*, 1955, **44**, 660.) Solutions of the material under test were placed on a column prepared from equal quantities of Solka-floc and Celite 545. The column was washed with water, followed by ethanol (27 per cent.) and again with water to remove impurities. A quantity of 5N acetic acid was then added to the column to elute the reserpine. A pair of platinum wires placed at the outlet of the column and connected to a voltmeter and a battery was used to show when the acetic acid (containing reserpine)

had reached the outlet. This solution was collected and assayed by determination of the ultra-violet absorption at 267 mμ. The method was found to be simple to use, and suitable for the routine assay of liquid preparations and tablets. G. B.

Sodium Carboxymethylcellulose, Non-aqueous Titration Assay For. C. N. Sideri and A. Osol. (*J. Amer. pharm. Ass., Sci. Ed.*, 1955, **44**, 759.) Sodium carboxymethylcellulose was assayed for sodium by heating with glacial acetic acid, cooling to room temperature and titrating with 0·1 N perchloric acid in dioxan. Slightly higher results were obtained by ignition of the sample before titration. These results were somewhat lower than those obtained by precipitating carboxymethylcellulose as a copper derivative and determining the copper content of it. Results based on sulphated ash determinations were higher, possibly because of the presence of iron and other substances in addition to sodium sulphate in the residue. G. B.

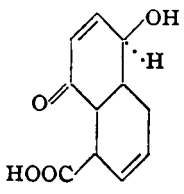
ORGANIC CHEMISTRY

Reserpine, Total Synthesis of. R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey and R. W. Kierstead. (*J. Amer. chem. Soc.*, 1956, **78**, 2023.) The total synthesis of reserpine (I) is briefly outlined.



(I)

The adduct from *p*-benzoquinone and vinylacrylic acid was reduced by sodium borohydride to the alcohol (II) which was converted to an oxide with



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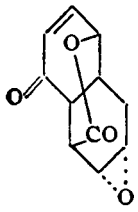

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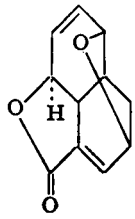

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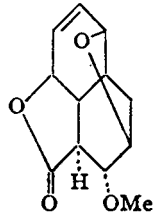
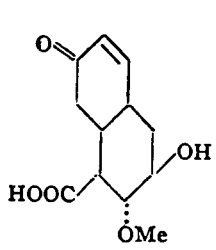


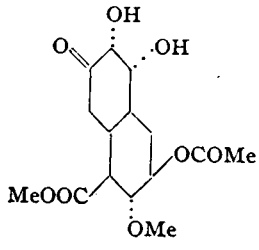
(V)

perbenzoic acid. Action of acetic anhydride and sodium acetate in benzene on the oxide gave the lactone (III) which was transformed by aluminium *iso*-propoxide in hot *iso*propyl alcohol into the ether (IV) and thence by the action of sodium methoxide in methanol to the methoxy-ether (V). The bromohydrin obtained by the action of *N*-bromosuccinimide on (V) in warm aqueous solution

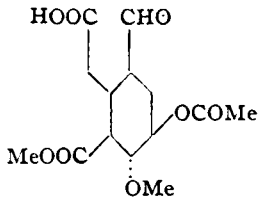
in the presence of sulphuric acid, was oxidised by chromium trioxide in acetic acid to a bromo-ketone which gave the hydroxy acid (VI) upon short treatment



(VI)

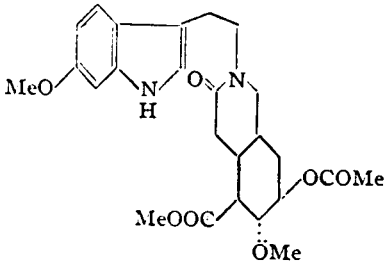


(VII)

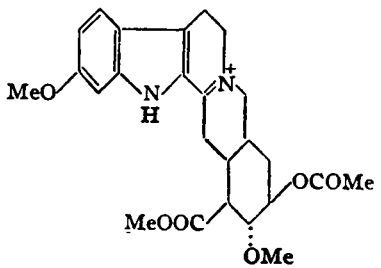


(VIII)

with zinc in cold glacial acetic acid. The methyl ester of (VI) was converted to the acetate by acetic acid in warm pyridine and thence to the diol (VII) by treatment with aqueous osmium tetroxide followed by potassium chlorate. The diol (VII) was transformed without isolation of the labile intermediates, e.g. (VIII) etc. to the lactam (IX), through successive treatments with aqueous periodic acid in ethereal diazomethane, condensation with 6-methoxytryptamine in benzene, and reduction with sodium borohydride in methanol. Boiling phosphorus oxychloride converted the lactam (IX) into the quaternary cation (X)



(IX)



(X)

which was reduced directly with aqueous methanolic sodium borohydride to (±)-methyl *O*-acetyl*iso*reserpate; resolution yielded (−)-methyl *O*-acetyl*iso*-reserpate. Hydrolysis with methanolic potash followed by treatment with hydrochloric acid to yield *iso*reserpic acid hydrochloride and then warming with *NN'*-di*cyclo*hexyl-carbodiimide yielded *iso*reserpic acid lactone. Isomerisation of the lactone with pivalic acid in boiling xylene gave reserpic acid lactone. Upon methanolysis this lactone yields methyl reserpate which can be transformed by 3:4:5-trimethoxybenzoyl chloride in pyridine to reserpine (I).

A. H. B.

BIOCHEMISTRY

GENERAL BIOCHEMISTRY

5-Hydroxytryptamine in Serum. D. F. Sharman and F. M. Sullivan. (*Nature, Lond.*, 1956, **177**, 332.) It is well known that 5-hydroxtryptamine (5-HT) is liberated from platelets during the clotting of blood and that the amount found in the serum varies according to the way in which the material is prepared.

The purpose of this paper was to investigate this variation. Human blood withdrawn from a vein in the arm by means of a silicone-treated syringe was used. The blood was allowed to clot either by placing it in a glass test-tube and letting it stand without agitation for 30 minutes or by placing it in a test-tube containing a glass marble and tipping the tube through $\pm 20°$ from horizontal at a rate of 15 cycles/minute for 30 minutes. In each case the clotted blood was centrifuged at 3000 rev./minute for 30 minutes, by which time the serum was free of platelets. Acetone extracts of the serum were assayed on the isolated uterus of the rat. The results indicated that agitation during the clotting results in a decreased amount of 5-HT in the serum. In another experiment it was shown that the clot does not adsorb 5-HT and that mechanical disturbance after clotting, even in the presence of the clot, does not destroy it. M. M.

Oxytocin and Vasopressin, Separation of. R. Hausmann. (*Arch. Pharm. Berl.*, 1956, **289**, 15.) By the action of pepsin on the protein hormone of pituitary posterior lobe, increasing amounts of the hormone peptide investigated by du Vigneaud are obtained. Glacial acetic acid also produces quantitative splitting. The resulting solutions may be separated by chromatography on paper, the position of the active principles being determined by biological tests on individual strips of the paper. Since vasopressin has an isoelectric point of 10·85, while that of oxytocin is 7·7, separation by high voltage ionophoresis is possible and indeed preferable to chromatography, since it is more rapid and there is less destruction of the activity. This is however only possible after a preliminary purification, e.g., by precipitation with ammonium sulphate. After separation by ionophoresis further purification can be achieved by paper chromatography. G. M.

Sarin, Enzymatic Hydrolysis of. F. C. G. Hoskin. (*Canada. J. Biochem. Physiol.*, 1956, **34**, 75.) The high toxicity of the organophosphorus cholinesterase inhibitors makes it difficult to study their metabolism and excretion in the intact animal. An investigation of the metabolism of *iso*propyl methylphosphonofluoridate (sarin) by rat serum enzyme has shown it to be hydrolysed to the less toxic *iso*propyl methylphosphonic acid. When this compound, labelled with ^{32}P, was given to rats it was excreted unchanged in the urine. It is suggested that the metabolism of sarin by the rat would lead almost exclusively to *iso*propyl methylphosphonic acid. G. F. S.

BIOCHEMICAL ANALYSIS

5-Hydroxyindoleacetic Acid and 5-Hydroxytryptamine in Urine, Test for. G. Curzon. (*Lancet*, 1955, **269**, 1361.) A simple and rapid test is described for the detection of 5-hydroxytryptamine (5-HT) and its metabolite 5-hydroxyindoleacetic acid using paper chromatography. Fifty μl. of urine is applied at a point 5 cm. from the edge of a rectangular piece of Whatman no. 4 paper. The urine is applied in 10 μl. portions and dried by a warm current of air. Five μl. of a 1 mg. per ml. ethanolic solution of 5-hydroxyindoleacetic acid or of a 0·2 mg. per ml. aqueous solution of 5-HT may be applied in parallel with the urine spot and also a normal urine for comparison. The sheet is fastened in cylindrical form and stood for 45 minutes in about 100 ml. of solvent in a wide-necked jar. The solvent for 5-HT is 8 g. of sodium chloride dissolved in 100 ml. of water, and 1 ml. of glacial acetic acid is added for the detection of 5-hydroxyindoleacetic acid. The paper is dried in a

warm oven, sprayed with colour reagent (2 g. dimethylaminobenzaldehyde dissolved in 5 ml. of concentrated hydrochloric acid and 95 ml. water), and heated at 55–60° C. for 15 minutes. Normal urines show a strong yellow urea spot and weak spots in the indoxyl-sulphate, tryptophan, and indoleacetic acid positions. Urines containing 20 mg. or more per litre of 5-hydroxyindoleacetic acid show a further blue-grey spot. Urines containing at least 2 mg. per litre of 5-hydroxytryptamine show a blue spot. The method may be useful in the diagnosis of metastasing carcinoid. G. F. S.

Insulin, Paper Chromatography of. G. Grodsky and H. Tarver. (*Nature, Lond.*, 1956, **177**, 223.) A paper chromatographic technique for the isolation and determination of insulin in small amounts of tissue has been devised. The proteins were precipitated from the hashed tissue by the addition of trichloroacetic acid, and the precipitate extracted with a mixture of ethanol-water and concentrated hydrochloric acid. After adjusting the pH to 8·5 to 9·0, and filtering out any precipitate, the insulin was precipitated by the addition of a mixture of ethanol and ether (3:5). The precipitate, in aqueous-ethanolic hydrochloric acid, was applied as a streak of droplets to Whatman 3 MM paper and chromatographed using *n*-butanol, water, acetic acid (12:5:2). Under these conditions insulin moves with R_F 0·21. After drying, the paper was immersed for 10 minutes in a solution of bromophenol blue (0·05 per cent.) and mercuric chloride (1 per cent.) in 2 per cent. acetic acid. Excess dye was washed out with dilute acetic acid, the insulin streak cut out, reduced to shreds, extracted with aqueous-ethanolic hydrochloric acid, and the intensity of the colour at 470 mμ measured. The amount of insulin was determined by comparison with known standards similarly treated, linear relationships being obtained with 0·1 to 0·2 mg. Chromatographic examination of liver protein, ribonuclease, and serum proteins showed that none of these behaved as did insulin, though glucagon appears to have properties similar to insulin. The production of insulin in fœtal beef pancreatic slices in the presence and absence of oxygen was also examined. Glucagon appeared to have a direct effect on insulin production. J. B. S.

Insulin, Paper Chromatography of. A. Light and M. V. Simpson. (*Nature, Lond.*, 1956, **177**, 225.) R_F values have been determined for crystalline insulin on Whatman No. 1 paper in various solvent systems. 2-Butanol/1 per cent. acetic acid (1:1) gave the most discreet spots, 20 μg. of insulin being easily detectable. The R_F value in this system varied slightly with the amount of insulin applied to the paper and with the distance travelled by the solvent front. The technique was used to detect insulin in various crude fractions, obtained by the procedure of Romans *et al.*, with the proviso that salt is removed by dialysis prior to chromatography, and also that excessive amounts of crude protein are not applied to the paper. The amount of insulin was estimated approximately by comparison with known insulin spots. Ribonuclease, serum album, or pancreatic fractions depleted of insulin showed no movement, but crystalline glucagon moved at the same R_F as insulin. Its presence in insulin samples may be detected by paper electrophoresis at pH 7·5. For preparative processes the use of Munktell No. 20 electrophoresis paper permitted insulin to move at its normal R_F even when the paper was heavily loaded with crude material. In a large-scale experiment 32 mg. of labelled insulin were isolated from 80 g. of calf pancreas slices which had been incubated in the presence of DL-leucine-1-^{14}C. J. B. S.

Isoniazid, Microdetermination of. J. Wagner, P. Kraus and B. Večerek (*Československ. Farm.*, 1955, **4**, 389.) A method for the determination of isoniazid in solutions, tablets or blood serum is based on its reaction with potassium mercuric iodide in alkaline solution to form a yellowish green turbidity which changes to orange-green on acidification. To 0·5 ml. of test solution (containing 4 to 20 μg. of isoniazid) 0·5 ml. of a 5 per cent. aqueous solution of potassium mercuric iodide and 1 ml. of N sodium hydroxide solution are added; after 1 minute the solution is acidified with 2 ml. of 2N acetic acid (to eliminate interference due to ammonium salts) and, after a further 5 minutes, the density of the turbid solution is measured in a 5-cm. cuvette in a Pulfrich photometer fitted with a S47 filter. The concentration is determined from a calibration graph constructed with solutions containing 8 to 40 μg. per ml. of isoniazid; over this range the optical density is proportional to the concentration. Determinations can be carried out directly on blood serum, previously deproteinised with barium hydroxide and zinc sulphate, but internal standards must be used in making the calibration graph. The error is $\pm$ 5 to 8 per cent. Hydrazine salts, phenylhydrazine and 2:4-dinitrophenylhydrazine react in the same way as isoniazid. E. H.

Phenobarbitone, Metabolite of, in Human Urine. E. J. Algeri and A. J. McBay. (*Science*, 1956, **123**, 183.) The *p*-hydroxy-derivative of phenobarbitone has been found in the urine of two patients who died after overdoses of phenobarbitone. The urines were extracted with ether at pH 7, the ether extracts washed with 0·2 N hydrochloric acid, dried with anhydrous sodium sulphate and shaken with 0·05 N sodium hydroxide until all the barbiturate was extracted. The ultra-violet absorbencies were measured at pH 9·5 and 2. The barbiturates were then re-extracted with ether from acid solution, the volume reduced and the ether solution submitted to paper chromatography. Two barbiturates were found; one located at R_F 0·5 was phenobarbitone, and the other at R_F 0·29 *p*-hydroxyphenobarbitone. In the first case the concentration of *p*-hydroxyphenobarbitone was 9·2 mg./100 ml. of hydrolysed urine and the barbiturate concentration of the blood 7·2 mg./100 ml. Forty-six per cent. of the *p*-hydroxyphenobarbitone was in the conjugated form. Similar results were obtained in the second case. G. F. S.

Staphylococcus Enterotoxin, Detection of. L. Levi, B. H. Matheson and F. S. Thatcher. (*Science*, 1956, **123**, 64.) The results are described of an infra-red spectrophotometric examination of boiled and lyophilised preparations obtained from cultures of enterotoxigenic and non-enterotoxigenic staphylococci (*Micrococcus pyogenes var. aureus*) in accordance with the "cold-ethanol" method developed by Thatcher and Matheson (*Can. J. Microbiol.*, 1955, **1**, 40). The specimens were finely powdered and 5 mg. was mixed intimately with 995 mg. of potassium bromide; 200 mg. of the mixture was then subjected in a vacuum to a pressure of 10,000 lb/sq. in. for about 5 minutes. The absorbancy of the clear disc thus produced, over the frequency range extending from 4000 to 650 cm.$^{-1}$, showed strong N–H and characteristic C–H stretching vibrations at 3400 cm.$^{-1}$ and 2900 cm.$^{-1}$, respectively. Marked absorptions noted at 1650 and 2540 cm.$^{-1}$ were indicative of the presence of polypeptide bonds, while the characteristic band occurring at 1065 cm.$^{-1}$ could be considered to be associated with ester linkages such as –C–O or C–O–P. The 1100 to 1000 cm.$^{-1}$ region proved to be the most informative, for the intensity of the absorption bands at 1065 cm.$^{-1}$ was always found to be higher for preparations showing enterotoxigenic activity than it was for preparations that were biologically inactive. R. E. S.

CHEMOTHERAPY

2-Amino-1 : 3 : 4-thiadiazoles, the Carcinostatic Activity of. J. J. Oleson, A. Sloboda, W. P. Troy, S. L. Halliday, M. J. Landes, R. B. Angier, J. Semb, K. Cyr and J. H. Williams. (*J. Amer. chem. Soc.*, 1955, **77**, 6713.) The carcinostatic activity of several 2-R-amino-1 : 3 : 4-thiadiazoles (where R = H, Me, Et, Allyl, Phenyl, Acetyl groups) against several transplanted animal tumours in mice is reported. The activity of 2-amino-5-R-1 : 3 : 4-thiadiazoles (R = OH, SH, Cl) and 2-R-amino 5-methyl-1 : 3 : 4-thiadiazoles (R = Me and Allyl) is also recorded. The parent compound, 2-amino-1 : 3 : 4-thiadiazole was the most active; the lower 2-alkylamino and 2-acetylamino derivatives were also active and less toxic than the parent compound, while the 2-phenylamino derivative was inactive. In most cases, substitution in the 5-position reduced the activity of the 2-amino derivative. A. H. B.

***iso*Nicotinyl Hydrazones from D-Mannuronolactone and D-Mannuronic Acid.** C. H. Brown, H. E. Bond, S. A. Peoples and P. P. T. Sah. (*J. Amer. pharm. Ass., Sci. Ed.*, 1955, **44**, 591.) Alginic acid was hydrolysed by heating under reflux with formic acid for 20 hours. Formic acid was removed by distillation, and the resulting D-mannuronolactone recrystallised from warm water. D-Mannuronic acid *iso*nicotinyl hydrazone was obtained by the reaction of D-mannuronolactone with isoniazid in hot water, and crystallised by allowing to stand overnight in a refrigerator. D-Mannuronolactone *iso*nicotinyl hydrazone was made similarly, but absolute ethanol or methanol was used as the solvent, so as to prevent hydrolysis of the product. The LD50 dose, determined by oral administration to mice was 1100 mg./kg. for the D-mannuronolactone derivative and 1000 mg./kg. for the D-mannuronic acid compound, compared with 160 mg./kg. for isoniazid. In *in vivo* tests in mice infected with *Mycobacterium tuberculosis* H37Rv, these derivatives appeared to be at least as effective as isoniazid. Results were very similar to those obtained with the corresponding D-glucuronolactone and D-galacturonic acid derivatives. G. B.

Spiramycin: Clinical and Laboratory Studies. D. G. Hudson, G. M. Yoshihara and W. M. M. Kirby. (*Arch. intern. Med.*, 1956, **97**, 57.) Laboratory and clinical studies of a new antibiotic, spiramycin, are presented. *In vitro* spiramycin effectiveness was determined by the inhibition of the growth of streptococci and pneumococci in tryptose phosphate broth containing three per cent. human blood, and of staphylococci in broth without added blood. Results were compared with those obtained simultaneously using penicillin and erythromycin at the same concentration. Antibiotic dilutions ranged from 0·01 μg. to 50 μg./ml. Spiramycin was the least active antibiotic in inhibiting the growth of pneumococci and β-hæmolytic streptococci, and generally so against staphylococci. With non-hæmolytic streptococci tested, spiramycin was less active than erythromycin but more effective than penicillin. Generally, the order of increasing sensitivity to spiramycin was: staphylococci; streptococci; pneumococci. Using 117 strains of freshly isolated streptococci, there appeared little evidence of cross resistance between spiramycin and either penicillin or erythromycin. *In vivo* studies involved 29 adult patients with bacterial pneumonia: 2·0 g. of spiramycin was given initially, followed by 1·0 g. every six hours. These oral doses were well tolerated and well absorbed, rapidly producing serum concentrations of 1·0 to 7·0 μg./ml., which are at least 100 times as great as those required to inhibit pneumococci *in vitro*. The clinical effectiveness of spiramycin against bacterial pneumonia appeared

comparable with results previously obtained at the same hospital using erythromycin and penicillin. No patients with staphylococcal infections were treated, but the low level of cross resistance suggests that spiramycin may be useful in the treatment of infections caused by penicillin- and erythromycin-resistant strains, although the relationship between inhibitory concentration *in vitro* and blood levels obtained, is less favourable than with erythromycin and penicillin.

G. P.

PHARMACY

NOTES AND FORMULÆ

Ergometrine Decomposition of Unstabilised Solutions of. J. Reichelt and L. Šafařík (*Československ. Farm.*, 1955, **4**, 404.) The effect of heat, atmospheric oxygen and ultra-violet light on unstabilised 0·1 per cent. solutions of ergometrine maleate at pH 3·5 to 4·0 is studied. The decomposition products are separated by chromatography on Whatman No. 1 paper; the paper is first impregnated with a solution of formamide in ethanol (4:6 or 3:7) and the chromatogram is developed with chloroform, saturated with formamide. Chromatography of solutions which had been aerated for 12 hours in the dark at room temperature shows that, in addition to ergometrinine, two decomposition products are produced; the first of these (X) showed a dark red fluorescence in ultra-violet light, and the second (Y) a yellowish green fluorescence. Neither of the substances reacts with *p*-dimethylaminobenzaldehyde. Ergometrinine and (+)-lysergic acid are the only decomposition products detected in solutions which had been heated to 100° C. in the absence of air for 15 hours. E. H.

Oxytetracycline and Tetracycline, Parenteral. M. Katz, O. Klioze and S. Y. P'an. (*J. Amer. pharm. Ass., Sci. Ed.*, 1955, **44**, 751.) Dry powders intended for the preparation of injections of oxytetracycline and tetracycline were made according to several formulæ, and the powders and solutions prepared from them were examined for stability. Potentiometric titrations and *in vivo* tests for absorption and irritation were carried out to assess the suitability of the preparations for injection. A mixture of oxytetracycline(terramycin)hydrochloride 1, sodium glycinate 0·9 was suitable for the preparations of solutions for intravenous or intramuscular injection. With a mixture of oxytetracycline hydrochloride 1, and magnesium chloride 1 it was possible to prepare solutions of concentrations up to 50 mg./ml., less irritating and better absorbed by intramuscular injection. A mixture of oxytetracycline hydrochloride 1, ascorbic acid 4 was suitable for preparing intravenous solutions more stable than those containing sodium glycinate. A solution prepared from a mixture of tetracycline hydrochloride 1, sodium glycinate 0·9 was suitable for intravenous but not for intramuscular injection. A solution for intramuscular injection was prepared from tetracycline hydrochloride 1, magnesium chloride 1, ascorbic acid 2·5, while an intravenous solution was prepared from a mixture of tetracycline 1 and ascorbic acid 3. The dry powders were stable when stored for 6 weeks at 50° C., and solutions retained most of their potency when kept for periods up to 72 hours at 25° C., although solutions of tetracycline were generally somewhat less stable than those of oxytetracycline. Intravenous solutions prepared with ascorbic acid were compatible with most transfusion fluids, including dextrose, sodium chloride and Ringer's solutions.

G. B.

PHARMACOLOGY AND THERAPEUTICS

Atropine in the Treatment of Anticholinesterase Intoxication. A. S. Gordon and C. W. Frye. (*J. Amer. med. Ass.*, 1955, **159**, 1181.) This paper re-emphasises the necessity for large doses of atropine in the treatment of intoxication resulting from antichloinesterase agents such as organic phosphate compounds used as insecticides. These compounds also have a potential use as chemical warfare agents, and military recommendations for treatment are as follows. In mild or moderate symptoms of poisoning 2 mg. of atropine sulphate should be injected intramuscularly. In severe cases 4 to 6 mg. should be injected intravenously or intramuscularly. After the initial dose 2 mg. should be given at hourly intervals or oftener until signs of atropinisation appear or as long as muscarinic effects are present. A review of reported cases of poisoning from these anticholinesterase agents reveals a direct relationship between survival, the amount of atropine given and the speed of administration. The consequences of inadequate treatment are grave, whereas the effects of excessive administration of atropine, though uncomfortable and occasionally temporarily incapacitating, are not serious. It is important to note that there is a marked tolerance for atropine in the presence of anticholinesterase poisoning, and the failure of appearance of atropinisation after a 2 mg. dose offers further presumptive evidence of anticholinesterase intoxication. An over-all survey of the literature includes almost 1000 people who have received atropine in excess of the usual therapeutic maximum of 1 mg.; most have received 2 mg. or more and about one-third more than 10 mg. Of this number only 11 persons have died. Details are given in the paper of 25 cases of anticholinesterase poisoning treated with atropine. Other measures necessary in the treatment of this type of intoxication are also outlined. S. L. W.

4-*n*-Butoxy β-(1-piperidyl) Propiophenone Hydrochloride and β-Diethylaminoethyl *p*-*n*-Hexyloxybenzilate Hydrochloride, Local Anaesthetic and Pharmacological Properties of. R. B. Arora and V. N. Sharma. (*J. Pharmacol.*, 1955, **115**, 413.) Dyclonine, [4-*n*-butoxy β-(1-piperidyl) propiophenone hydrochloride] and β-diethylaminoethyl *p*-*n*-hexyloxybenzilate hydrochloride were both effective topical local anæsthetics in a series of ophthalmological surgical procedures in guinea-pigs. The benzilic acid ester was the more potent, but was slower in onset and more irritant. There was no parasympathomimetic or anticholinergic activity with either substance. On intravenous injection into anæsthetised dogs small doses of both drugs stimulated respiration and caused a fall in arterial pressure; with increase in dose (3 to 5 mg./kg.) respiration was depressed. The reduction in blood pressure was due both to a decrease in cardiac output and to a direct arteriolar dilatation; both compounds increased flow through the vessels of the isolated hind limbs of dogs. Intestinal motility was reduced in anæsthetised dogs with the benzilate, but not with dyclonine. In man, dyclonine, in a concentration of 1 per cent., and the benzilate in a concentration of 0·25 per cent., produced analgesia in ophthalmic operations, equivalent to that of a 4 per cent. solution of cocaine hydrochloride. G. P.

Calcium Methionate, Pharmacological Study of. G. V. Rossi, T. S. Miya and L. D. Edwards. (*J. Amer. pharm. Ass., Sci. Ed.*, 1956, **45**, 47.) Calcium chloride, gluconate and methionate were submitted to comparative trial in rabbits, rats and mice. Equimolecular concentrations produced similar effects on the blood pressure, smooth muscle (ileum and uterus) and diaphragm, the

effects being those characteristic of calcium compounds, and independent of the anion present. Calcium methionate was shown to be slightly more toxic than calcium gluconate, but produced the same effects on gross appearance, growth rate, blood picture, bone composition and tissue morphology in rats. Calcium methionate was effective in raising the blood calcium level in rats, and was slightly more rapidly absorbed and removed from the blood than calcium gluconate. It has the advantage of greater solubility, and solutions of high calcium content may be prepared without stabilisers. Solutions are suitable for oral or intravenous administration, but are too irritant for injection by the subcutaneous and intramuscular routes. G. B.

Chlorpromazine, Antagonism of 5-Hydroxytryptamine by. E. P. Benditt and D. A. Rowley. (*Science*, 1956, **123**, 24.) 5-Hydroxytryptamine (5-HT) or a related substance was found to be associated with mast cells in rat tissue and was liberated along with histamine by histamine-liberators such as ovomucoid, compound 48/80 and dextran. 5-HT produced hyperæmia and œdema after subcutaneous injection into the dorsum of the rat's paw; the extent of the response was indicated by azovan blue dye, injected into the tail vein immediately before administration of the 5-HT. Dibenamine antagonised these actions. Chlorpromazine (1·0 to 1·5 mg./kg. i/v) also antagonised the actions of 5-HT in this preparation and in addition antagonised similar actions of histamine. On the isolated rat's colon chlorpromazine in a concentration of about 10^{-6} antagonised the stimulant actions of both acetylcholine and 5-HT; recovery from this inhibitory effect was complete only after 30 minutes. G. P.

Chlorpromazine in the Treatment of Tetanus Convulsions. R. E. Kelly and D. R. Laurence. (*Lancet*, 1956, **270**, 118.) The object of this study was to discover a drug or combination of drugs which will abolish the muscle spasm of tetanus without affecting respiration or abolishing consciousness. Of a number of drugs tried on experimental tetanus the only ones of any promise were chlorpromazine and promethazine. Chlorpromazine was shown to be effective against rabbit tetanus in a dose of 1 mg./kg. body weight. This dose abolished "spontaneous" tetanus and reflex tetanus for an average of 77 minutes; if no afferent stimulus was applied the tetanus was abolished for periods up to twice as long. The animals were quiescent after this dose, but normal rabbits would hop about if encouraged. Respiration was unaffected. Promethazine also abolished tetanus but only in high dosage and for a shorter time. A child, aged 2½ years, with severe tetanus convulsions, was successfully treated by means of chlorpromazine alone given by intravenous infusion. Chlorpromazine was given for 16 days, the total daily dose, in mg./day, being 75, 180, 220, 200, 155, 225, 285, 275, 330, 250, 215, 300, 240, 115, 50, 30. The degree of control varied, but opisthotonic spasms occurred no more than three or four times a day, and minor spasms lasting less than 15 seconds ten to fifteen times a day. At no time was consciousness lost as a result of administering the drug. The child was always easily roused from sleep. Respiration was unaffected. Considerable intravenous thrombosis occurred and 10 mg. of heparin was added to each bottle of infusion. An intravenous drip was kept going throughout the period of chlorpromazine administration, the solutions used being at first 5 per cent. dextrose and then compound sodium lactate injection B.P., of which about 500 ml. was given each day. Large doses of tetanus antitoxin were given at the start, and penicillin to prevent respiratory complications. The child had a slow but uneventful convalescence. S. L. W.

Ergot Drugs, Effect of, on *Betta splendens*. L. T. Evans, L. H. Geronimus, C. Kornetsky and H. A. Abramson. (*Science*, 1956, **123**, 26.) The hallucinogenic drug, (+)-lysergic acid diethylamide, (LSD-25), induced a quiescent state in the Siamese fighting fish, *Betta splendens*; changes in the behavioral, vegetative and motor characteristics of the fish were seen when the drug was added to the aquarium water in a concentration of 5×10^{-7} M. Eight other ergot derivatives were also tested for these effects; only two, a monobromo derivative (BOL-148), and (+)-lysergic acid ethylamide (LAE-32), had activity approaching that of LSD-25. Among those with negligible activity were ergotamine, dihydroergotamine, (−)-LSD-25 and (+)-*iso*-LSD-25. Mescaline and pethidine were also tested and also had negligible depressant activity. G. P.

Ethinamate, The Pharmacology and Toxicology of. E. E. Swanson, R. C. Anderson and W. R. Gibson. (*J. Amer. pharm. Ass., Sci. Ed.*, 1956, **45**, 40.) Ethinamate (ethynyl*cyclo*hexyl carbamate, Valmid, Valamine) was tested for hypnotic action and toxicity in mice, rats and dogs. For oral administration an emulsion with 5 per cent. of acacia was used. A solution in polyethylene glycol 200 was given by intravenous injection. Electroencephalographic studies indicated that the mode of action of ethinamate is similar to that of barbiturates. Duration of hypnotic effect in rats and dogs was about half that of quinalbarbitone sodium. The ratio of hypnotic and toxic doses was approximately the same as for quinalbarbitone sodium. Ethinamate showed some protective action against electric shock and leptazol and some local anæsthetic effect. It had no antipyretic, analgesic or diuretic action. Liver appeared to play a role in the degradation of the drug, since rats with liver damage showed a prolonged sleeping time whereas nephrectomised rats did not. Intravenous injection of ethinamate into dogs previously anæsthetised with the same substance lowered the blood pressure and slowed the heart rate and respiration, eventually causing death from respiratory failure unless this was prevented by artificial respiration or administration of picrotoxin. G. B.

Glycyrrhizinic Acid, Preparation of, and Effects in Man. L. H. Louis and J. W. Conn. (*J. Lab. clin. Med.*, 1956, **47**, 20.) A method is described for the preparation of ammonium glycyrrhizinate, the sodium retaining principle from liquorice. When administered orally to ten normal subjects it had no effect upon protein or carbohydrate metabolism, nor was there any effect upon the renal excretion of uric acid and creatinine, or upon the level of circulating eosinophils. There were very significant effects upon electrolyte metabolism, the most intense being upon the retention of sodium and chloride. There was only a mild increase in the urinary potassium. A patient with Cushing's syndrome reacted similarly, but there was no effect upon the electrolyte metabolism in two cases of congenital hyperplasia. Ammonium glycyrrhizinate depressed the excretion of 17-ketosteroids, particularly in normal subjects with high levels of 17-ketosteroid excretion and in the patients with congenital adrenal hyperplasia. It also decreased the concentrations of sodium and chloride in thermal sweat, and it is capable of inhibiting the pituitary release of the melanophore stimulating hormone; the effect of 4 g. per day orally being roughly equivalent to 37·5 mg. of cortisone, 20 mg. of hydrocortisone and 5 mg. of 9-α-fluorohydrocortisone orally. The results suggest that ammonium glycyrrhizinate acts in the body very similarly to an adrenal steroid. Its peripheral effects are exclusively upon electrolyte and water metabolism, but it can depress both production of the adrenocorticotrophic and melanophore stimulating hormones. G. F. S.

Isoniazid, Streptomycin and PAS; Combined Use in Tuberculous Meningitis. R. Maggi, C. J. G. Diaz and F. C. Pfister. (*Antibiotic Med.*, 1956, **2**, 21.) Twenty children, with tuberculous meningitis, whose ages ranged from 1 to 11 years, were treated with combined therapy as follows. Isoniazid by mouth, 15 to 20 mg./kg./day was administered in three divided doses. Streptomycin, 30 mg./kg./day, was given by intramuscular injection every 12 hours. PAS in a 3 per cent. solution in triple distilled water was given by venoclysis in a dose of 0·5 to 0·6 g./kg./day in severe cases, and in other cases optionally by mouth every 6 hours with daily doses of 0·4 g./kg. body weight. This treatment was continued for 2 to 3 months, and was followed by maintenance treatment which lasted about 4 months and comprised the simultaneous use of two drugs with the basic and permanent treatment of streptomycin intramuscularly, given at intervals of 48 hours (later, 72 hours), and isoniazid by mouth 8 to 10 mg./kg./day in 2 divided doses, alternating every 4 weeks with PAS by mouth 0·4 g./kg./day in 4 divided doses. Of the 20 patients, 11 received extrathecal treatment exclusively, while the rest were treated in addition with intralumbar streptomycin injections in doses of 1 to 2 mg./kg./day. Comparison of the results between the two groups of children appeared to indicate distinct advantages for the extrathecal method of treatment. The mortality of the intrathecal group was 3 out of 9, whereas on the extrathecal group only 1 out of the 11 patients died. The clinical and humoral response of the latter group was also more prompt, and the frequency of blocks was considerably lower. The authors conclude that exclusive extrathecal therapy is not only possible but appears to be the method of choice. The prolonged use of isoniazid in this series did not cause any disagreeable side reactions or toxic symptoms.

S. L. W.

Mercaptomerin, Systemic Reactions to. W. C. Smallwood and H. L. Matthews. (*Lancet*, 1956, **270**, 121.) Four patients had systemic toxic reactions to subcutaneous injections of mercaptomerin. In three of the patients the reactions appear to have been allergic (the symptoms including fever, rigor, malaise, cyanosis, dyspnœa, and erythematous rash), while the fourth patient developed hæmorrhagic colitis, probably due to excretion of metallic mercury through the wall of the gut. These 4 cases were collected within a period of 2 years from a hospital with 120 medical beds, which suggests that systemic reactions to mercaptomerin may not be rare. The drug was given as directed by the makers. The 4 cases were under treatment when different consignments of the drug were in use in the hospital. Other patients treated with the same batches of mercaptomerin were not affected. In their time-relationship to the giving of the injection and in the prominence of cyanosis and circulatory collapse the reactions in these patients were very similar to those described following the use of other mercurials. Certain characteristics of these reactions suggest an allergic mechanism; they rarely follow the initial dose of the drug and their severity increases with each successive dose and is unrelated to the size of the dose. It appears that the effect of the first few doses is to sensitise the patient and that later doses induce an allergic response. In most cases and initially the response is mild, but if the mercurial is continued even in small doses violent and dangerous reactions may follow, as in two of the cases reported. The authors conclude that mercaptomerin can cause generalised systemic reactions which do not appear to differ from those caused by other organic mercurial diuretics given by other routes.

S. L. W.

Mustine in the Treatment of Malignant Effusions. A. S. Weisberger, B. Levine and J. P. Storaasli. (*J. Amer. med. Ass.*, 1955, **159**, 1704.) Forty-

three patients with pleural, pericardial or peritoneal effusions due to metastatic malignant disease were treated with mustine. Immediately prior to mustine therapy the patients were given 0·2 g. of quinalbarbitone and 50 mg. of chlorpromazine. In the patients with pleural and peritoneal effusions the mustine was administered in a single injection of 0·4 mg./kg. body weight. In 2 patients with pericardial effusion doses of 10 mg. and 22 mg. of mustine were used respectively. The mustine was prepared immediately preceding injection by adding 10 ml. of isotonic sodium chloride to each 10 mg. ampoule. In the treatment of peritoneal effusion a paracentesis was done and half the fluid removed. While there was still a free flow of fluid the mixture was administered either through a catheter inserted into the trocar or through a needle introduced at another site. A similar procedure was followed for the intrapleural and intrapericardial administration, except that the mustine was introduced directly through the needle used to remove the fluid. After administration of the mixture the patient was changed to a new position every 5 or 10 minutes for a period of an hour to ensure more uniform distribution of the material throughout the serous cavity. On the following day paracentesis was repeated and as much fluid removed as possible. The patients were followed closely with X-rays and physical examinations for evidence of reaccumulation of fluid. Of the 43 patients, 28 (65 per cent.) were significantly improved. In 20 of the 28 there was no reaccumulation of fluid; in 8 of the patients there was a marked reduction in the amount of fluid reaccumulating. Twenty of the 28 patients were still living at the time of the report, with improvement lasting from 6 to 24 months in 10 patients and 2 to 5 months in 10 patients. The best responses were obtained in patients with carcinomas of the breast or ovary. In this series the leukopenia following mustine therapy was very mild and much less than that following intravenous therapy with mustine. Nausea and vomiting were also minimal. This suggests that larger and more effective doses of mustine could be used without adverse side-effects. The results compare favourably with those obtained with radioactive colloidal gold and all patients with effusions due to metastatic malignancies should be given a trial of mustine therapy. S. L. W.

Neomycin in Urinary Tract Infections. R. J. Roantree and L. A. Rantz. (*Antibiotic Med.*, 1956, **2**, 103.) *In vitro* studies showed neomycin to be a particularly effective antibacterial agent against the *Escherichia coli*, paracolon, *Proteus*, and *Aerobacter* groups of bacilli; it was found ineffective against *Pseudomonas*. Neomycin was administered intramuscularly to 20 patients having urinary tract infections resistant to most of the other antibiotics. Except in 2 cases the dosage did not exceed 1 g./day and the duration of treatment was 5 days or less. The clinical result was gratifying in most cases. In those cases in which the urinary tract infection was the chief disease the fall in temperature and relief of symptoms was usually prompt. 15 of the 20 patients had sterile urine cultures immediately after treatment, though there were a number of reinfections later; the 5 other patients had *Pseudomonas* in their urine following treatment. No permanent damage to the kidney or to the eighth cranial nerve was noted in this series. This confirms previous observations that neomycin given in a dosage of 1 g. daily for 5 days or less does not result in toxic residual effects if the patient has normal renal function. If there is intrinsic renal disease resulting in nitrogen retention it is probably wise not to use neomycin. Neomycin is a useful agent for the treatment of urinary tract infections if it is reserved for those cases in which the organisms are resistant to less toxic drugs. S. L. W.

Phenoxymethylpenicillin: Plasma Penicillin Levels. R. L. Nichols, W. F. Jones and M. Finland. (*Proc. Soc. exp. Biol., N.Y.*, 1955, **90**, 688.) This paper presents comparisons of penicillin levels in plasma after administration of phenoxymethylpenicillin and benzylpenicillin. The subjects were 8 normal young men and 24 hospital patients, with ages ranging from 15 to 86, all of whom had normal renal function. Three dosage forms of penicillin were used, namely: (1) the free acid of phenoxymethylpenicillin in 200,000 unit tablets, (2) buffered potassium benzylpenicillin in 200,000 unit tablets, and (3) aqueous potassium benzylpenicillin intramuscularly. These were given at 3 dosage levels, namely, 200,000 units, 400,000 units and 1,000,000 units; individual doses were separated by at least 48 hours. All subjects received both the oral penicillins at least at one and the same dosage level and many also received an intramuscular injection of the same number of units of benzylpenicillin. Three of the young men received all 3 dosage forms at all 3 levels, and 5 subjects received all 3 dosage forms at each of the 3 levels. The results of the assays showed that oral phenoxymethylpenicillin gave higher and better sustained levels of penicillin activity in the plasma than oral buffered potassium benzylpenicillin at each of the 3 dosage levels. Intramuscular potassium benzylpenicillin yielded higher and better sustained levels than oral phenoxymethylpenicillin in equivalent doses of 400,000 or 1,000,000 units. An intramuscular dose of 200,000 units of potassium benzylpenicillin produced higher peak levels and these occured earlier, but were less well sustained, than with this amount of oral phenylmethoxypenicillin; the total amount of penicillin absorbed from this amount of penicillin was not significantly different for these 2 dosage forms. Persons over 60 attained peak levels later and, in general, had higher and better sustained levels of penicillin in the plasma from any given dose than did younger individuals. S. L. W.

Propoxyphene, Bioassay of Analgesic Activity of. C. M. Gruber, E. P. King, M. M. Best, J. F. Schieve, F. Elkus and E. J. Zmolek. (*Arch. int. Pharmacodyn.*, 1955, **104**, 156.) A controlled clinical study is reported of the analgesic activity of propoxyphene (α-(±)-2-propionoxy-4-dimethylamino-1:2-diphenyl-3-methyl-butane hydrochloride), compared with codeine phosphate, acetylsalicylic acid and a placebo, in patients with chronic pain. The drugs were given orally in identical capsules, containing approximately equiactive doses at two dose levels, one or two capsules every four hours, and in a randomised order. A complete "series" was one day on each drug and one day on placebo. At the end of each twenty-four hour period, when the drugs were changed, the patients were asked to estimate the number of hours of pain at each of four intensities (severe, moderate, slight or none), which were scored for evaluation. A statistical analysis showed the following to be significant (1) the variation among patients, (2) the variation among the drugs (entirely due to placebo) and (3) between the two doses of the placebo. Significant differences were not found between the analgesics or surprisingly between the doses of the analgesics. Since pain is subjective, the difference between the estimates of pain with the placebo and with the drugs may be used to determine the relief of pain according to the formula:—

$$\text{Per cent. pain relief} = \text{Placebo} - \text{Drug} \times 100 \div \text{Placebo}.$$

The slopes of the lines were almost parallel and there was no important difference in the pain relief between the drugs at the following dose levels, which are concluded to have the same analgesic activity—propoxyphene 50 mg., codeine phosphate 32·5 mg., and acetylsalicylic acid 325 mg. There was also no significant difference in side effects. G. F. S.

Radioactive Digitoxin, Metabolic Fate of, in Human Subjects. G. T. Okita, P. J. Talso, J. H. Curry, F. D. Smith and E. M. K. Geiling. (*J. Pharmacol.*, 1955, **115**, 371.) Biosynthetically-labelled ^{14}C-digitoxin was given intravenously, in multiple doses, to three patients whose prognoses were poor. Doses were between 0·1 and 0·5 mg.; the last dose was administered between 16 hours and 36 hours before death. Autopsies were performed within two hours of death and tissue samples assayed for both unchanged digitoxin and its metabolic products. Heart muscle showed no particular affinity for the glycoside, in comparison with other organs. The kidney and the contents of the gall bladder, jejunum, ileum and colon had the highest concentrations of unchanged digitoxin. The gall bladder contents, jejunum contents and the spleen were associated with high concentrations of the metabolic products. The liver had the greatest total amount of both the glycoside and its metabolites. It was also the main site of detoxification of the drug: most of the administered glycoside was metabolised in the body. The probable fate of injected digitoxin is as follows: after intravenous injection there is an initial rapid removal of the drug from the bloodstream; the drug is metabolised, during and after this time, in the liver and passes into the gastrointestinal tract *via* the biliary tract; it is to a large degree reabsorbed from the small intestine and enters the enterohepatic cycle; the kidney meanwhile excretes small quantities of the metabolites and lesser amounts of the unchanged drug. The kidney is the major excretory site for the drug and its metabolites. G. P.

Thiuram Disulphides and Related Compounds, Acute Toxicity and Disulfiram-like Activity. B. A. Barnes and L. E. Fox. (*J. Amer. pharm. Ass., Sci. Ed.* 1955, **44**, 756.) Several thiuram disulphides and related compounds were tested for toxicity in mice and for ability to induce acetaldehydæmia in rabbits. Di*cyclo*hexylthiocarbamoyl diethylthiocarbamoylsulphide,bis(dibutylthiocarbamoyl)sulphide and bis(di*iso*butylthiocarbamoyl)disulphide had approximately the same activity as disulfiram, while being less toxic. The presence of two amino groups and double-bonded sulphur appeared to be essential for disulfiram-like activity. A possible explanation is that the $\rangle C = S$ group inhibits acetaldehyde metabolism by linking to the enzyme in competition with the substrate, but that in order to have a sufficiently high activity a substituted amino group must be present. Ascorbic acid did not have any effect on the metabolism of ethanol nor on the ability of disulfiram to inhibit the metabolism of acetaldehyde. G. B.

3:5:3′-Tribromo-DL-Thyronine in Myxœdema. N. Compston and R. Pitt-Rivers. (*Lancet*, 1956, **270**, 22.) This study was undertaken not in anticipation of any therapeutic advantage of tribromothyronine over other thyroxine analogues but because the demonstration of high thyroxine-like activity of non-iodine containing analogues of thyroxine in man must cause a reorientation of views on thyroid physiology. Two patients with primary myxœdema were treated with tribromothyronine and both responded fully to a daily dose of 1 mg. of this compound given by intramuscular injection. In both cases normality was maintained, after treatment with tribromothyronine had been stopped, with 4 gr. of thyroid daily. From this it would appear that 1 mg. of DL-tribromothyronine is equivalent to 0·4 mg. of L-thyroxine. It may be assumed from previously published evidence that the D-isomer in DL-tribromothyronine is virtually inactive in human myxœdema. It therefore appears that tribromothyronine has only slightly less activity than thyroxine itself since 1 mg. of the DL-compound (containing 500 μg. of the L-isomer) had activity equivalent to 4 gr. of desiccated thyroid. S. L. W.