ABSTRACTS OF PAPERS PUBLISHED IN OTHER JOURNALS

CHEMISTRY

ANALYTICAL

Copper in Oils and Fats, Determination of. D. C. Abbott and R. D. A. Polhill. (*Analyst*, 1954, **79**, 547.) A method is reported for the rapid determination of copper in oils and fats over the range 0·02 to 2 parts per million by means of dibenzyldithiocarbamic acid and its salts. The fatty matter is mostly removed from the sample by vaporisation and the remainder is destroyed by digestion with nitric and sulphuric acids. The copper in the resulting acid solution is then determined, after dilution, by the extraction of its dibenzyldithiocarbamate with carbon tetrachloride and the absorptiometric measurement of the resulting solution at 435 mμ in a suitable spectrophotometer. The preparation of the dibenzylammonium, potassium, and zinc salts is described. Recovery results for added copper, by comparison with a direct acid extraction method, were good; both the method described and direct extraction with hydrochloric acid and nitric acids at 100° C. gave complete recovery of copper added as the oleate to two oils. For critical work, wet combustion is to be preferred owing to the possibility of extraction difficulties. R. E. S.

Phenolphthalein in Chocolate Preparations, Determination of, by Non-aqueous Titration. S. Doernberg, M. Hubacher and I. Lysyj. (*J. Amer. pharm. Ass., Sci. Ed.*, 1954, **43**, 418.) For the non-aqueous titration of phenolphthalein, a mixture of 15 per cent. of ethylenediamine with 85 per cent. of pyridine is better than a simple solvent, giving a sharp reproducible end-point without the formation of a precipitate. The determination should be performed in an enclosed system, so as to exclude water and carbon dioxide. A suitable titration solution may be prepared by dissolving sodium in ethanolamine, diluting with pyridine and standardising against benzoic acid. The following method is recommended for the analysis of chocolate preparations. Grate a chilled sample containing about 0·1 g. of phenolphthalein, remove the fat with carbon tetrachloride and extract the phenolphthalein with acetone. Evaporate the acetone solution to dryness, dissolve the residue in 30 ml. of pyridine-ethylenediamine solution, and titrate to the yellow-green colour with thymol blue indicator. Continue the titration to the electrometric end-point. The difference represents the quantity of reagent equivalent to the phenolphthalein. Results compare favourably with those by the gravimetric method. G. B.

Total Penicillins, Assay of. M. Gordon, A. J. Virgona and P. Numerof. (*Analyt. Chem.*, 1954, **26**, 1208.) An isotope dilution assay for total penicillins in broth is described using sulphur-35 labelled penicillin followed by the isolation of the *N*-ethyl piperidine salt; degradation of penicillin was unnecessary and penicilloic acid did not interfere. 14 analyses of a lyophilised broth showed results in substantial agreement with those obtained by chemical or microbiological assay; the limits of error (P = 0·95) were ± 5·9 per cent. on the mean of duplicate assays. Samples containing a total of 10,000 units in a convenient volume could be assayed by this procedure. R. E. S.

Vitamin B_{12} and Other Cobalamins, Assay of. F. A. Bacher, A. E. Boley and C. E. Shonk. (*Analyt. Chem.*, 1954, **26**, 1146.) A number of general techniques are outlined for the assay of vitamin B_{12} in complex mixtures ranging from fermentation products to vitamin capsules, by the purification and concentration of the vitamin; the methods of extraction and purification, when applied to a variety of fermentation products and other mixtures, yielded aqueous solutions sufficiently pure for the spectrophotometric determination of cyanocobalamin. Other cobalamins can be determined after conversion to vitamin B_{12}. Radio-active vitamin B_{12}, introduced as an aqueous solution of purified cyanocobalamin containing radio-active cobalt, was used as a tracer to determine recovery through the various extractions necessary for purification. A combination of purification operations can be selected to fit each type of sample; a general description is given for the conversion and addition of the tracer, zinc defecation, cresol-butanol extraction, acid-cresol-butanol extraction, cresol-butanol-benzalkonium extraction, dicyanide complex-benzalkonium extraction, and resin column treatment. Samples containing 100 μg. of vitamin B_{12} at concentrations as low as 0·1 μg. per ml. can be assayed. In a series of difficult assays a standard deviation of $\pm$ 4·3 per cent. was found. R. E. S.

Vitamin D, Determination of, in the Presence of Vitamin A. D. T. Ewing, T. D. Schlabach and M. J. Powell. (*Analyt. Chem.*, 1954, **26**, 1406.) A method is given for the determination of vitamin D_2 in oil samples containing less than 50,000 units/g. The method involves a two-step chromatographic process, a Superfiltrol column being used to remove vitamin A, carotenoids, pigments, some sterols, and irradiation products of ergosterol other than vitamin D_2; the second chromatographic step uses activated alumina to remove certain unsaturated compounds of the squalene type, certain vitamin A decomposition products, residual impurities from the Superfiltrol adsorbent, and other materials present in the non-saponifiable portion of vegetable oils. Vitamin D which is eluted from the adsorbent column is finally determined by measuring the absorbance at 265 mμ rather than by the use of antimony chloride reagent. The shape of the absorption curve of vitamin D in the region of 265 mμ is a valuable criterion of the purity of the compound. Marked distortion of the absorption curve is indicative of the probable presence of an impurity which may introduce an error. The method has been successfully applied, within the stated limits, to samples of crystalline vitamin D_2 and vitamin A acetate in corn oil, irradiated ergosterol and vitamin A palmitate in corn oil, some fish oils, and some miscellaneous samples. R. E. S.

GLYCOSIDES, FERMENTS AND CARBOHYDRATES

Digitalis Glycosides, Chemical Assay Process. D. H. E. Tattje. (*Ann. pharm. franc.*, 1954, **12**, 267.) Each stage of the Keller-Kiliani process for determining digitoxose in the digitalis glycosides has been investigated by the author, who then recommends the following reagent: aqueous solution of $FeCl_3,6H_2O$, 5 per cent., 1 ml.; water 1·5 ml.; concentrated sulphuric acid, 5 ml.; glacial acetic acid up to 100 ml. Maximum colour intensity is attained after 10 minutes and remains constant for 60 minutes. The density is read at 600 mμ. Because of the comparatively large proportion of water present in the reagent, it is claimed that slight variations in water content would be practically without effect. J. W. F.

Digitoxin, Comparative Study of the Assay of. H. A. Braun and L. M. Lusky. (*J. Amer. pharm. Ass., Sci. Ed.*, 1954, **43**, 440.) Assays by the U.S.P. XIII pigeon method were compared with those by the U.S.P. XIV colorimetric method which depends upon the development of an orange-red colour in the presence of an alkaline picrate solution (Baljet reaction). Two samples of commercial digitoxin glycoside gave results 26 and 30 per cent. higher by the colorimetric, as compared with the biological method, apparently owing to the presence of substances such as gitoxin, possessing the unsaturated lactone groups required for colour formation, accompanied by less biological activity than digitoxin. The discrepancy was greater when some tablets of digitoxin were assayed, because of the presence of magnesium stearate, used as an excipient. The substance caused turbidity in the solutions, resulting in increased light absorption. This source of error may be removed by centrifuging the solution to remove the turbidity. G. B.

Glycosides and Carbohydrates, Chromatographic Detection of. J. A. Cifonelli and F. Smith. (*Analyt. Chem.*, 1954, **26**, 1132.) A method is described for the detection of non-reducing glycosides on a paper chromatogram. The paper is first sprayed with a weak periodate solution whereby the α-glycol grouping is split and, at the same time, the periodate ion is reduced to iodate; on spraying with benzidine, the glycosides are located by the appearance of white spots on a blue background, the latter arising from the oxidising action of periodate on benzidine. Details of procedure are given for the differentiation of ketoses from other reacting carbohydrate compounds by spraying with a modified benzidine reagent and for the differentiation of reducing sugars from non-reducing carbohydrates. The R_F values are tabulated for 32 carbohydrates together with the colour reactions shown in the various modified tests. R. E. S.

BIOCHEMISTRY

GENERAL BIOCHEMISTRY

Adrenaline and Noradrenaline, Blood Platelets as Carriers of. H. Weil-Malherbe and A. D. Bone. (*Nature, Lond.*, 1954, **174**, 557.) Experiments are described which were designed to determine whether or not differences between chemical and biological methods of determining adrenaline in blood plasma could be explained by the different methods of blood collection. In the biological method precautions were taken to prevent platelet breakdown, whereas no such precautions had been taken in applying the chemical method. A comparison of the two methods shows that the substances estimated as adrenaline and noradrenaline by the chemical method are associated to a large extent with the blood platelets. When platelet disintegration is avoided about 70 to 80 per cent. may be removed from the plasma by centrifuging, and a considerable part may be recovered from the platelet residue. The fraction previously regarded as "plasma" adrenaline, unlike the adrenaline of the red blood corpuscles, undergoes rapid and extensive changes in response to such stimuli as injection of hormones and drugs, and stimuli produced by convulsions and sleep. J. B. S.

Inorganic Anions, Heparin-like Activity of Certain. J. H. Bragdon and R. J. Havel. (*Science*, 1954, **120**, 113.) Phosphotungstate, phosphomolybdate and silicotungstate ions delay the clotting of blood both *in vitro* and *in vivo*. In the *in vivo* experiments rats were given the compound intravenously in doses of 20 mg. dissolved in 1 ml. of 0·15 M sodium chloride, using either the acid

or the sodium salt. Sodium silicotungstate was found active when given by mouth in doses of 200 mg. The heparinoid action was apparent a few minutes after intravenous injection and 20 minutes after oral administration. Lee-White clotting times were prolonged 2 to 5 times. The substances produced in the plasma "lipæmia clearing factor," an enzyme catalysing the lipolysis of chylomicrons and low-density lipoproteins. As with heparin, the anticoagulant activity was inhibited by protamine, clearing activity was inhibited by protamine and by sodium chloride and the compounds showed metachromatic activity with toluidine blue. H. T. B.

Vitamin B_{12} in Crude Liver Extracts. F. A. Robinson, M. E. H. Fitzgerald, K. Fehr and J. J. Grimshaw. (*Nature, Lond.*, 1954, **174**, 558.) Evidence has been obtained that some of the vitamin B_{12} in crude liver extracts cannot be assayed by means of the *E. coli* mutant. Binding of cyanocobalamin by crude liver extracts has also been observed. It has been shown, using the *E. coli* mutant, that the apparent vitamin B_{12} content of these liver extracts increases on boiling, and that only a proportion of added cyanocobalamin can be accounted for when using *E. coli* for assay. The optimum treatment to liberate the bound vitamin in the liver extract was 4 hours boiling. On standing again for a few days the apparent vitamin B_{12} content falls to its original value. The results suggest that crude liver extracts contain a vitamin B_{12} binding substance. The microbiological activity of extracts is not increased by treatment with cyanide. Bound vitamin B_{12} can be dialysed slowly through a "Cellophane" membrane. Digestion with papain or trypsin does not increase the activity of extracts, although pancreatin significantly enhances activity. The binding of vitamin B_{12} in liver extracts is quite different from the behaviour of cyanocobalamin in the presence of an intrinsic factor concentrate from hog stomach. Boxet and Richards' conclusion that "in liver concentrates, cyanocobalamin usually accounts for only a small fraction of total cobalamins" has been confirmed. J. B. S.

BIOCHEMICAL ANALYSIS

Barbituric Acids in Body Fluids, Determination of. P. Lous. (*Acta pharm. tox. Kbh.*, 1954, **10**, 134.) The ultra-violet absorption spectrum of barbituric acid differed from that of dialyl-substituted barbituric acids. The extraction of barbituric acid, barbital, phenobarbital and aprobarbital from aqueous solutions with chloroform was shown to depend on *p*H, barbituric acid itself being only slightly extracted. Results were obtained, both by the gravimetric method of Halstrom (*Om. Stifidentifikation i den Forensiske Kemi*, 1940, Copenhagen) and by the spectrophotometric method, on samples of human sera to which known amounts of barbital, phenobarbital and aprobarbital had been added; on sera obtained from cases of acute barbituric acid poisoning; and on urines from human subjects after administration of these barbiturates. Satisfactory agreement was found between the two methods in all cases with the exception of aprobarbital, where the spectrophotometric result was higher than the gravimetric. R. E. S.

Iron in Serum and Blood, Determination of. H. W. Josephs. (*J. Lab. clin. Med.*, 1954, **44**, 63.) The method is based on the colour reaction of ferric iron with ammonium thiocyanate and the author claims to have eliminated various sources of error in the techniques previously suggested. The determination can if necessary be carried out on as little as 0·5 ml. of serum or 0·1 ml. of

whole blood. The serum is heated with diluted hydrochloric acid to liberate iron combined with globulin, protein is then precipitated with trichloroacetic acid, and the iron is oxidised to the ferric state by means of nitric acid. Subsequent procedure varies with the colorimeter to be used. In the procedure suggested ethyl acetate is added followed by the thiocyanate reagent and the depth of colour of the separated ethyl acetate layer is determined in an Evelyn colorimeter with micro attachment. A blank determination is also made. As in other methods involving protein precipitation, calculation of the result involves the assumption that the iron is distributed in equal concentration between the protein precipitated and the supernatant liquid. For whole blood, the same procedure is applied to a solution obtained by "ashing" the blood with sulphuric acid in a Kjeldahl flask. H. T. B.

Scilliroside in Organic Material, Detection of. F. Dybing, O. Dybing and K. B. Jensen. (*Acta pharm. tox. Kbh.*, 1954, **10**, 93.) A method for the identification of scilliroside, the active principle of red squill, using paper chromatography (*Acta pharm. tox. Kbh.*, 1953, b. **9**, 99) is described. For detection on the chromatogram trichloroacetic acid, antimony trichloride, and Liebermann's reagent were used, the sensitivities of these tests ranging from 1 to 10 μg. scilliroside. The paper chromatographic method was combined with biological demonstration of scilliroside in mice, amounts of 10 to 15 μg. scilliroside being easily detected. Details are given for the isolation of scilliroside from organic material, the extracts being purified on the basis of systematic examinations of the distribution between water and organic solvents. The method was employed for the detection of scilliroside after experimental poisoning in rats and rabbits, amounts of 100 μg. of scilliroside being demonstrated in about 200 g. of liver. R. E. S.

PHARMACY

NOTES AND FORMULÆ

Antimould Agents for Syrups. C. F. Lord Jr. and W. J. Husa. (*J. Amer. pharm. Ass., Sci. Ed.*, 1954, **43**, 438.) "Mycophil agar" was melted and mixed with deteriorated syrup containing micro-organisms and an ethanolic solution of the preservative under test. The mixture was allowed to set in a Petri dish, incubated for up to 6 days at 28 to 29° C. and examined for the growth of moulds. The effect of the preservative was assessed by comparison with a control plate prepared with ethanol instead of the solution under test. Mould growth was inhibited by 0·1 per cent. of benzoic acid, 0·01 per cent. of cinnamic aldehyde or 0·001 per cent. of oxyquinoline sulphate. Many volatile oils, including those used in flavouring and perfumery were shown to inhibit the growth of moulds. G. B.

Iothiouracil Sodium (Itrumil Sodium). *New and Nonofficial Remedies, J. Amer. med. Ass.*, 1954, **155**, 444.) Iothiouracil sodium is sodium 5-iodo-2-thiouracil, $C_4H_2IN_2NaOS$. It occurs as an odourless, white to light yellow, crystalline powder, m.pt. 235° to 240° C., soluble, at 25° C., in 28 parts of water, and 200 parts of ethanol; *p*H of a 2 per cent. solution, 8·5 to 9·5. It is usually obtained as the dihydrate, which is reasonably stable to moisture and sunlight at room temperature. It yields violet vapours when heated with sulphuric acid, and a neutral buffered solution gives a green colour 5 to 10 minutes after the addition of Grote's reagent. When a solution in water is treated with glacial acetic acid, a precipitate of 5-iodo-2-thiouracil is obtained, which,

after washing with water and ethanol, and drying *in vacuo*, melts at 220° C. to 225° C., with decomposition. Iothiouracil sodium contains not more than 20 p.p.m. of heavy metals. The loss in weight on drying at 105° for 5 hours does not exceed 14·0 per cent. (dihydrate), 7·5 per cent. (monohydrate), or 3·0 per cent. (anhydrous). It contains 98·0 to 102·0 per cent. of anhydrous iothiouracil sodium when assayed by titration with 0·1 N iodine in buffered neutral solution, using mucilage of starch as indicator, and 43·7 to 48·3 per cent. of iodine, which is estimated by boiling a solution with potassium permanganate and sulphuric acid for 15 minutes, adding an excess of silver nitrate solution, removing the excess of permanganate with sodium sulphite, and weighing the precipitate of silver iodide after purification and drying. Iothiouracil sodium exhibits the thyroid-involuting effect of iodine and the antithyroid action of thiouracil, but has not been shown to be superior to non-iodinated derivatives administered concomitantly with iodine. G. R. K.

Polyethylene Glycol as Binder in Tablet Compression. B. Miller and L. Chavkin. (*J. Amer. pharm. Ass., Sci. Ed.*, 1954, **43**, 486.) The use of polyethylene glycol as a dry binding agent makes possible the preparation of a wide range of tablets economically by the double compression process. The preliminary "slugging" may be carried out rapidly in a high-speed rotary tablet machine, since high pressure is unnecessary. Polyethylene glycol (macrogol) 4000 and 6000 appear to be equally suitable, best results being obtained by the use of the material after passing it through a No. 80 sieve. In experiments on phenacetin tablets, the most satisfactory formula contained 15 per cent. of dried maize starch, 2 per cent. of calcium stearate and 20 per cent. of polyethylene glycol 4000. The tablets obtained by double compression had a hardness of 3 kg. (Monsanto hardness tester) and a disintegration time of 20 minutes by the U.S.P. method. Salicylates, which lower the melting point of polyethylene glycols, cause sticking of the material to the punches. Formulæ are given for the preparation of tablets of dried aluminium hydroxide gel, calcium lactate, thyroid, ferrous sulphate, sodium bicarbonate and extract of cascara sagrada. The method may be used in many instances where moist granulation is unsuitable or inconvenient. G. B.

Polyethylene Glycol in Tablet Coating. E. H. Gans and L. Chavkin. (*J. Amer. pharm. Ass., Sci. Ed.*, 1954, **43**, 483.) Compressed tablets were placed in a coating-pan and a primary coating of a 25 per cent. solution of polyethylene glycol (macrogol) 6000 in ethanol at 50° C. was applied. After drying the coating in warm air, further quantities of the 25 per cent. solution were applied to build up a thin translucent coating, the thickness of which was then increased by the application of successive quantities of a 50 per cent. solution of polyethylene glycol 6000 in ethanol at 50° C. The coating was hardened by heating the tablets to 50–55° C. for 3 hours, after which polishing was carried out with a wax solution. The process showed a considerable saving in time compared with conventional sugar coating, only 4 to 5 hours being required to build up the coating or slightly longer when deep concave punches had been used. Polyethylene glycol coatings proved to be non-hygroscopic and at least as stable as sugar coatings when subjected to shaking tests and storage at 45° C. and 100 per cent. relative humidity. Coloured coatings were readily obtained by the use of coloured 40 per cent. solutions of polyethylene glycol 6000 in ethanol, applied before the hardening and polishing process. Since ethanol was used as the solvent, protective undercoats were not necessary when dealing with substances affected by water. G. B.

PHARMACOLOGY AND THERAPEUTICS

Adrenaline and Noradrenaline Content of Human Adrenal Glands. U. S. von Euler, C. Franksson and J. Hellström. (*Acta physiol. scand.*, 1954, **31**, 6.) Adrenal glands removed from patients suffering either from carcinoma or from hypertension contained about 85 per cent. adrenaline and 15 per cent. noradrenaline. No difference either due to the age of the patient or to the clinical condition could be detected. M. M.

Amino-alcohol Esters of *p*-Nitro and *p*-Amino-benzoic Acids. R. Hazard, A. H. Nezamie, E. Corteggiani, P. Chabrier and S. Larno. (*Thérapie*, 1954, **9**, 324.) The methyl iodide of the diethylaminoethanol ester of *p*-amino-benzoic acid has been shown to have a marked nicotinic effect on the blood pressure of the chloralosed dog (Hazard *et al.*, *C.R. Acad. Sci.*, 1943, **216**, 779). Furthering these studies, the esters of *p*-amino- and *p*-nitro-benzoic acid with dimethylamino-, piperidinyl- and morpholinyl-ethanol have been prepared as the hydrochlorides and methyl iodides. These were examined for vasopressor effects on the chloralosed dog under artificial respiration. The *p*-nitrobenzoic esters had no nicotinic actions. In the series of *p*-aminobenzoic esters only those of dimethyl-amino-ethanol showed appreciable nicotinic action, those of the other two amino-alcohols having little or no activity. The formation of the quaternary salts (i.e. the methyl-iodides) increased nicotinic actions where these were already present and gave rise to this property in some compounds hitherto inactive. The methyl-iodides also potentiated the vasopressor action of adrenaline. G. P.

Bis-Fluorenyl-Bis-Quaternary Ammonium Compounds, Curare-like Activity of. F. J. Macri. (*Proc. Soc. exp. Biol., N.Y.*, 1954, **85**, 603.) 3 compounds of a series of polymethylene bis-(fluorenyl-dialkyl)-quaternary ammonium salts were compared with *d*-tubocurarine chloride for curarising activity. 2 were hexamethylene derivatives and the third decamethylene. The comparison was made by the mouse inclined screen test, by the rabbit head-drop test and on the sciatic nerve-gastrocnemius muscle preparation of the dog. On mice all 3 compounds were less effective than *d*-tubocurarine. Replacement, in the hexamethylene analogue, of the *N*-ethyl radicals by *N*-methyl radicals, slowed markedly the rate of absorption from subcutaneous injection and decreased curariform activity. With rabbits the two hexamethylene compounds were more potent than, and the decamethylene derivative of equal potency to, *d*-tubocurarine. On the gastrocnemius of the dog the two hexamethylene compounds had the same curariform activity as *d*-tubocurarine. Again the decamethylene derivative was less active than the other two. Qualitative characterisation of hexamethylene bis-(fluorenyl-dimethylammonium bromide) in the dog showed its neuromuscular blocking action to be antagonised by decamethonium and neostigmine. Also the compound did not block stimulation of the peripheral end of the vagus, but in large doses caused a fall in heart rate and blood pressure in the anæsthetised, artificially respired dog. The nicotinic action of acetylcholine on the blood pressure after atropinization was potentiated by this compound. G. P.

Cardiac Glycosides, Pharmacology of. K. Chen and F. Henderson. (*J. Pharmacol.*, 1954, **111**, 365.) The lethal dose of 64 cardiac glycosides, aglycones and their derivatives is determined using cats and their relative potency tabulated. The importance of spatial arrangement in the molecule is stressed. M. M.

Chloramphenicol and Oxytetracycline, Studies on. W. W. Faloon, J. W. Noll and K. Collins. (*J. Lab. clin. Med.*, 1954, **44**, 75.) Nitrogen balance, riboflavine excretion, fat absorption and liver histology and function were studied in 4 patients during treatment with chloramphenicol and in 5 patients during treatment with oxytetracycline. Two of the patients receiving chloramphenicol and 3 of those receiving oxytetracycline had cirrhosis of the liver. Chloramphenicol produced no changes in nitrogen balance, fat absorption, riboflavine excretion or liver function. The histologic appearance of the liver as shown by biopsy, if changed at all, was slightly improved. Administration of oxytetracycline resulted in an increase in nitrogen excretion in 4/5 patients; in the remaining patient, nitrogen excretion fell when the antibiotic was stopped. Urinary excretion of riboflavine increased correspondingly, decreasing when administration of the drug ceased. Fat excretion was not increased. No significant changes were found in liver function or histology. In one patient given chlortetracycline the observed effects were similar to those produced by oxytetracycline. Further studies on two patients indicated that the increased nitrogen excretion following treatment with oxytetracycline is not affected by the sodium intake. The effects of the administration of the two antibiotics are unrelated to the presence or absence of cirrhosis. H. T. B.

Chlorpromazine in Psychoneuroses. G. Garmany, A. R. May and A. Folkson. (*Brit. med. J.*, 1954, **2**, 439.) A clinical investigation of the effects of chlorpromazine on 29 psychonuerotics was undertaken. The patients were given 25 mg. by mouth three times daily, the dose being raised by 25 mg. every other day to a maximum of 75 mg. three times daily. In many cases the optimum effect was attained with 50 mg. three times daily. Maximum clinical improvement may be expected after 4 to 6 weeks of treatment, and thereafter a daily maintenance dose of 50 to 100 mg. is necessary. All the cases in which tension was predominant were much improved; of the 29 patients, 18 showed a significant degree of relief from tension. Patients with notable hysterical features, those with mainly phobic features, and those with mainly depressive features did badly. Results in 5 patients with predominantly obsessional features were poor. The results of this investigation did not confirm the value which has been claimed for the drug in "psychasthenic" illness, though its value in the treatment of tension states appears to have been adequately established. Toxic effects on the liver were noted in a few cases following the appearance of pyrexia after 7 to 10 days of treatment, and in 2 cases of hypertension an alarming tachycardia was observed. S. L. W.

***iso*Cytosines, Diuretic Activity of.** C. G. van Arman. (*J. Pharmacol.*, 1954, **111**, 285.) A series of 34 *iso*cytosine compounds were investigated for diuretic activity. The most active one, 5-methyl-6-phenyl*iso*cytosine, was found to be about 360 times more potent than urea in the rat but only weakly active in the dog, by the oral route. The mode of action resembles that of the xanthines. M. M.

1-*cyclo*Hexyl-1-phenyl-3-pyrrolidino-1-propanol Methylsulphate (Compound 14045) Pharmacology of. H. M. Lee, W. Gibson, W. G. Dinwiddie and J. Mills. (*J. Amer. pharm. Ass., Sci. Ed.*, 1954, **43**, 408.) Experiments *in vivo* showed that 1-*cyclo*hexyl-1-phenyl-3-pyrrolidino-1-propanol methylsulphate has a powerful anticholinergic action, being more effective when injected intravenously than when given by mouth. It inhibited the action of methacholine on isolated strips of guinea-pig ileum, and exhibited an antispasmodic action

on the gastrointestinal tract of trained dogs and anæsthetised dogs and cats. Other effects observed included vagus blocking, mydriatic action and inhibition of salivary secretion in dogs and suppression of the spontaneous secretion of gastric juice in rats. At high dosage levels, blocking of sympathetic ganglia and nerve-muscle conduction were observed, The substance protected guinea-pigs from the effects of an aerosol of methacholine iodide. Acute toxicity tests in mice, rats and dogs showed that the substance is approximately as toxic as atropine when given orally and rather more toxic when injected intravenously. In 3-month feeding tests, the substance was well tolerated by rats and dogs.

G. B.

Lead Poisoning, Treatment of, by Chelation. L. H. Cotter. (*J. Amer. med. Ass.*, 1954, **155**, 906.) Four cases are described as typical of a series of 26 patients treated by the administration of disodium calcium ethylenediamine tetra-acetate. The four patients were painters exhibiting typical symptoms of chronic lead poisoning. Before treatment, a thorough biochemical examination was made, including the determination of serum copper, sodium, calcium, magnesium and phosphorus. Treatment was begun with a test dose of 250 mg. given by mouth. If no allergic symptoms were observed at the end of 24 hours, the dose was repeated every two hours to a total of 2 g., and this was continued for a week, each patient thus receiving 14 g. The drug was pleasant to take and produced no complaints; most patients reported an urge to urinate about 15 minutes after a dose. Symptoms usually began to subside shortly after the commencement of treatment, and recovery was uneventful. Repetition of the biochemical examination after one month showed that the levels of serum calcium, copper, sodium and magnesium were not significantly altered. Two patients of the series showed a rise in total serum inorganic phosphate, and two showed a rise in serum copper. The serum cholesterol was the slowest in returning to normal. G. R. K.

Methonium Compounds, Tolerance to Ganglion Blockade by. J. K. Mohanty. (*Nature, Lond.*, 1954, **174**, 184.) The mechanism whereby tolerance to the ganglion-blocking action of methonium salts is developed, has been studied. No tolerance was observed when methonium compounds were administered to isolated autonomic ganglia, but similar isolated preparations taken from whole animals, which had previously been made tolerant by repeated doses, were found to have become almost insensitive to these compounds. Application of blood from tolerant animals conferred tolerance on isolated ganglia from non-tolerant animals. It was also observed that ganglia of eviscerated or dehepatised cats did not develop tolerance, except in those cross circulation experiments where the isolated liver of another animal was incorporated into the circulation. Incubation of hexamethonium with liver homogenates rapidly led to its total disappearance, and the resulting solution applied to isolated ganglia, produced resistance to the further effects of hexamethonium. The liver principle which inactivated hexamethonium is thought to be an enzyme and has been isolated in comparatively pure state. About 60 per cent. of hexamethonium administered parentally is excreted in the urine, the remainder being metabolised by the liver.

J. B. S.

Nickel Poisoning. F. W. Sunderman and J. F. Kincaid. (*J. Amer. med. Ass.*, 1954, **155**, 889.) Exposure of about 100 workmen to the vapour of nickel carbonyl necessitated hospital treatment for 31. Initial symptoms included dizziness with severe headache, nausea, shortness of breath, and a

dry cough. The time of onset of severe symptoms varied from 10 hours to 8 days after exposure and was usually manifested by a paroxysm of coughing, accompanied by extreme weakness and ready fatigue; artificial respiration was necessary for some patients. One patient died 4 days after exposure. Nickel carbonyl poisoning was diagnosed on the fourth day and thereafter the remaining patients were given dimercaprol, in a dosage of 2·5 mg./kg. of body weight every 4 hours for a total of 6 doses. One other patient died, 13 days after exposure, but the administration of dimercaprol was considered beneficial in most of the remainder, and may have been life-saving in several. Five other cases are also reported. Two of these were subjected to only slight exposure and exhibited no symptoms, although the concentration of nickel in the urine rose from the normal value of 1·1 μg. per 100 ml. to 11 and 18 μg. per 100 ml. Two others exhibited moderate symptoms, but all four recovered without treatment. The fifth patient received dimercaprol the day following exposure. The urine collected on this day contained 1900 μg. of nickel per 100 ml. but rapidly returned to normal. No further treatment was required. G. R. K.

Polyvidone, Urinary Excretion of. A. W. Wilkinson and I. D. E. Storey· (*Lancet*, 1954, **266**, 1269.) Solutions of polyvidone (polyvinylpyrrolidone) are used as a plasma substitute. The urinary excretion of the compound, which is not metabolised in the body, has been measured in 20 postoperative patients. In 5 patients more than 70 per cent. of the polyvidone injected was recovered; in 9 others 50 to 70 per cent.; in 5 patients 40 to 50 per cent. and in 1 case less than 30 per cent. There was no relationship between the quantity of polyvidone administered and the quantity excreted in the urine. Determination of the rate of excretion showed that patients fell into 4 groups. In the first group (5 patients) each excreted more than 50 per cent. of the dose within 24 hours. In the second group (13 patients) 30 to 40 per cent. was excreted in the first 24 hours while in the third group less than 10 per cent. was excreted in 24 hours and only 30 per cent. in 80 hours. At the height of excretion the urinary concentration was usually 1 to 2 per cent., but higher concentrations, up to 5 per cent., were also found. The differences may be due to a postoperative oliguria and to the proportion of low molecular weight material in the preparation. G. F. S.

Pyridoxine, Effect of, on the Action of Isoniazid. J. Ungar, E. M. Tomich, K. R. Parkin and P. W. Muggleton. (*Lancet*, 1954, **267**, 220.) Isoniazid given in repeated doses of 75 to 200 mg./kg. causes retardation of normal growth-rate and involution of the thymus and testes in rats, and reduces the rate of conception in rats and guinea-pigs. Pyridoxine in a dose of 3·2 mg./kg. daily restored normal conditions of growth. Experiments were conducted to establish that pyridoxine when used to alleviate the side-effects occurring during isoniazid treatment in man does not interfere with its antituberculous action. *In vitro* experiments with virulent human-type bacilli showed that the inhibitory effect of isoniazid on the cultures was unaffected by any concentration of pyridoxine. *In vivo* tests were conducted on mice infected with a virulent strain of tubercle bacilli; four groups each of 20 mice were treated with isoniazid in varying doses and four control groups with the same doses with varying amounts of pyridoxine added. Post-mortem examinations showed that the pyridoxine did not affect adversely the curative power of isoniazid. It is suggested that pyridoxine could be tried without adverse effect in the isoniazid treatment of patients who show signs of intolerance to the drug. S. L. W.

Serotonin, Antimetabolites to. E. Shaw and D. W. Woolley. (*J. Pharmacol.*, 1954, **111**, 43.) In a series of indole derivatives examined for antiserotonin activity, a highly active group of compounds have been prepared by alkylation of the amino group of 2-methyl-3-ethyl-5-aminoindole. The most active of these were the dimethylamino analogue and the 1-methyl derivative of this which were both 250 times more active as serotonin antagonists than the parent amine, when tested on isolated carotid artery segments of the sheep. These two compounds also showed a high degree of antiserotonin activity on the uteri of rats in œstrus and on guinea-pig uteri. However, in the dog under pentobarbitone anæsthesia, although the dimethylamino analogue given orally over a period of a week caused a sustained fall in blood pressure, there was little or no antagonism of the vasopressor response to serotonin. The reason for this was not clear. Besides antiserotonin effects, in large doses it caused contraction of the rat uterus in œstrus, but not of the isolated carotid artery of the sheep. Also in mice, intraperitoneal injection induced clonic convulsions. These convulsions were not affected by the simultaneous injection of serotonin or its methyl ether. G. P.

Serotonin, Some Neurophysiological Aspects of. D. W. Woolley and E. Shaw. (*Brit. med. J.*, 1954, **2**, 122.) Serotonin (5-hydroxytryptamine), a vasoconstrictor substance formed in shed serum, has been found to occur in the brain, in the stellate and other visceral ganglia. Its function on the nervous system is now being discovered. It is possible that there is a functional participation of serotonin in the brain, particularly since a number of antiserotonin drugs cause mental aberrations and these mental changes may be the result of an interference with the action of serotonin in the brain. However, every antagonist of serotonin does not elicit the mental changes and serotonin does not overcome the neurological effects of the drugs, but it seems that serotonin does not penetrate the blood-brain barrier. Naturally occurring psychiatric states, such as schizophrenia, may be due to a deficiency of serotonin in the brain due to a failure of metabolic processes which normally synthesise it. The use of serotonin in these conditions may be indicated, but the failure of peripherally injected serotonin to penetrate the brain may make it necessary to devise compounds with serotonin-like activity which can penetrate. Alternatively, mental aberrations may arise from an excess of serotonin due to the failure of enzyme destruction, where the antiserotonin would compete with the enzyme—amine oxidase—rather than blocking the action of serotonin on the brain. Feldberg and Sherwood have shown that the direct introduction of serotonin into the latteral ventricle of the cat causes a behaviour rather like clinical schizophrenia. It is suggested that the quantitative measurement of serotonin in the cerebral fluids of mentally deranged patients would be valuable. G. F. S.

Substance P, Effects of Intraventricular Administration of. U. S. von Euler and B. Pernow. (*Nature, Lond.*, 1954, **174**, 184.) Tachypnœa and hypernœia produced by substance P injected into the third ventricle of the rabbit and the cat have been observed. Substance P (100–150 units/mg.) prepared and purified by the method of von Euler and Pernow was used. Solutions in Ringer were injected into anæsthetised animals through a cannula inserted in the intersection of the coronal and sagittal sutures at right angles to the vertex of the skull. Respiration was measured quantitatively using a body-plethysomograph. Intraventricular injection of five units of substance P produced, after a short latent period, a successively increased rate of respiration of 30 to 50 per cent.

with a maximal effect occurring after 10 to 15 minutes. The effect was more pronounced with 20 units. Increased amplitude of respiratory movement was also observed. A gradual rise of blood pressure (ca. 10 mm. Hg) was noted. A prominent tachypnœa and increased respiratory amplitude was also observed in unanæsthetised rabbits after injection of 10 units of substance P. J. B. S.

Succinylcholine, Clinical Use of. H. R. Griffith. (*Canad. med. Ass. J.*, 1954, **71**, 28.) The short duration of the action of succinylcholine makes it a much more controllable drug than other muscle relaxants. It probably acts by occupying receptor sites of voluntary muscles which are normally occupied by the acetylcholine produced in response to nerve impulses. Whereas acetylcholine is almost instantaneously hydrolysed by tissue cholinesterases, the succinyl compound is little affected by these enzymes and the termination of its action is probably due to hydrolysis by plasma pseudocholinesterases after rediffusion back into the blood stream. The onset of relaxation is indicated by fibrillary twitching in scattered muscle fibres throughout the body which is sometimes sufficiently marked to suggest impending convulsion but it lasts for only a few seconds. While a single intravenous injection of 40 to 60 mg. of succinylcholine in an adult produces relaxation for 2 to 3 minutes and is useful for procedures such as intubation or reduction of a dislocation, prolonged controllable relaxation is obtained by intravenous infusion of a dilute solution, using 500 mg. in 500 ml. of saline, the rate of infusion depending on the degree of relaxation required. The total dose may be from 50 to 900 mg. The drug is not an anæsthetic and the restless patient needs more anæsthetic, not more relaxant; the doses of the two must be adjusted to the needs of each case and vary widely. The long continued apnœa and flaccidity which have been reported after using the compound are probably the result of failure to adjust the dosage to the particular patient. Means to control respiration and instantly to provide pulmonary ventilation must be available. To the physician the drug is of value as an adjunct to shock therapy for psychiatric conditions and in the treatment of tetanus. It may be useful in convulsive states such as eclampsia, overdoses of local anæsthetics and strychnine poisoning. H. T. B.

Succinyldicholine and Succinylmonocholine, Urinary Excretion of, in Man. F. F. Foldes and S. Norton. (*Brit. J. Pharmacol.*, 1954, **9**, 385.) The urinary excretion of intravenously injected succinyldicholine was determined in 23 patients undergoing surgical procedures. The urine was collected up to 100 minutes after administration of the drug and the isolated frog rectus abdominus muscle used to estimate the urinary concentration. After single 1 mg./kg. doses an average of only 2·2 per cent. appeared in the urine. With continuous intravenous administration, sufficient to cause surgical relaxation, the urinary excretion was 2·8 per cent. Using a dose of succinylmonocholine equimolar to the 1 mg./kg. dose of succinyldicholine, the urinary succinylmonocholine averaged 9·2 per cent.; with this dose no neruomuscular block was apparent. Where the dose was increased to that causing relaxation, up to 14·5 per cent. was excreted in the urine. The "procaine esterase" activity of the plasma collected before administration of the relaxant bore some relation to the duration of apnœa induced by the drug, but not to the urinary excretion of either the succinyldi- or the succinylmono-choline. G. P.

Symmetrical Bis-Quaternary Ammonium Salts, Neuromuscular Blockade by. S. Thesleff and K. R. Unna. (*J. Pharmacol*, 1954, **111**, 99) The chicken sciatic nerve–gastrocnemius muscle preparation and the mouse inclined-screen

(ABSTRACTS *continued on page* 79.)