ABSTRACTS OF PAPERS PUBLISHED IN OTHER JOURNALS

CHEMISTRY

ANALYTICAL

Aloes, Composition and Assay of. H. Auterhoff and B. Ball. (*Arzneimitt.-Forsch.*, 1954, **4**, 725.) Pharmacological assay of aloes preparations on mice is unsatisfactory, as the dose required is relatively very much greater than with man. Trials were therefore made by using 45 volunteers, in order to test the comparative effect of different preparations. For the chemical determination of aloin, 20 mg. of the material was refluxed for 3 hours with 1 ml. of ferric chloride solution (25 per cent.) and 10 ml. of acetone and the solution was then evaporated to dryness. The residue was warmed with 20 ml. of *n*-butanol, and the solution was transferred to a separating funnel, with the aid of a little water, the flask being rinsed successively with 15 ml. of boiling hydrochloric acid (5 per cent.) and 15 ml. of boiling butanol. After shaking, the aqueous layer was rejected, the butanol phase being washed with 15 ml. of dilute hydrochloric acid and then filtered through cotton wool. The butanol solution was treated with 30 ml. of methanol, and made up to 100 ml. with a solution containing 5 per cent. of sodium hydroxide and 2 per cent. of ammonia. After standing for 15 minutes, 5 ml. was diluted with the above alkali to 100 ml. and the extinction was determined using a filter VG9 (owing to variations in shade, more accurate methods of photometry are undesirable.) The conclusions drawn were as follows: the aloin content, determined as above, is a measure of the laxative action on human subjects, although the results of trials with mice show a different picture. The action of preparations is determined by the aloin content. Aqueous and acetone extracts are comparable in action with the drug itself. Side effects are apparently less frequent with the aqueous extract than with the drug, but the view that this is also the case with the acetone extract is not confirmed. G. M.

Chloramphenicol, Colorimetric Determination of. W. Döll. (*Arzneimitt.-Forsch.*, 1955, **5**, 97.) 1 ml. of a solution of chloramphenicol and 4 ml. of sodium hydroxide (40 per cent.) is brought to the boil, resulting in a yellow colour apparently due to the sodium salt of *p*-nitrophenol. This colour is determined photometrically. The method may be applied directly to serum or blood, after the removal of protein with trichloroacetic acid. G. M.

Dihydrostreptomycin, Chemical Assay of. H. Vogt. (*Arch. Pharm. Berl.*, 1955, **288**, 20.) Dihydrostreptomycin is quantitatively precipitated by ammonium reineckate, 1 molecule of the dihydrostreptomycin combining with 3 molecules of reinecke acid. For the assay 5 ml. of a solution (containing about 10 mg. of dihydrostreptomycin sulphate) is treated with 5 ml. of a freshly prepared 2 per cent. solution of ammonium reineckate. After standing for 30 minutes in ice, the mixture is centrifuged: 5 ml. of the clear supernatant liquid is removed, diluted with 40 ml. of water and 2 ml. of Fehling's solution (No. 2), and hydrolysed on the water bath. The mixture is acidified with nitric acid, treated with a definite excess of 0·1 *N* silver nitrate solution, and titrated back with ammonium thiocyanate. A blank is done with 5 ml.

of water and 5 ml. of the ammonium reineckate solution. 1 ml. of 0·1 *N* solution is equivalent to 6·09 mg. of dihydrostreptomycin sulphate. In presence of procaine-penicillin the solution is first extracted with chloroform for 1 hour, chloroform being removed from the resulting solution by a current of air.

G. M.

Opium Alkaloids, Spectrophotometric Determination of. M. S. Dyer and A. J. McBay. (*J. Amer. pharm. Ass., Sci. Ed.*, 1955, **44**, 156.) Ultra-violet absorption spectra were determined for the principal alkaloids of opium from 240 to 330 mμ in solutions of varying *p*H. Absorption maxima suitable for quantitative analytical use were found in each case. Thebaine appeared to be unstable in the presence of hydrochloric acid but a solution in N sulphuric acid was stable and had a suitable spectrum. For the assay of papaveretum and similar products a method of analysis was evolved depending on solvent extraction to separate the alkaloids partially so as to obtain a series of solutions each containing two alkaloids, except that the narcotine was separated from all the others. The codeine/thebaine solution was analysed by measurements at 265 and 285 mμ, the morphine/narceine solution at 278 and 300 mμ, the papaverine/thebaine solution at 285 and 312 mμ, and narcotine at 312 mμ. From these results the total quantity of each alkaloid was calculated. G. B.

Parathion, Identification and Determination of. A. I. Biggs. (*Analyst*, 1955, **80**, 279.) The ultra-violet absorption spectra of parathion and its hydrolysis product *p*-nitrophenol have been studied. Parathion shows a well defined peak in 95 per cent. ethanol solution at 276 mμ, $\epsilon = 9630$; and in *n*-hexane at 268 mμ, $\epsilon = 10{,}350$, the spectrum being unaffected by acid or alkali. *p*-Nitrophenol shows, in ethanolic hydrogen chloride (0·001 N) a maximum at 314 mμ ($\epsilon = 10{,}750$) and in ethanolic potassium hydroxide (0·01 N) a peak at 408 mμ ($\epsilon = 20{,}830$). On heating 95 per cent. ethanolic solutions of parathion with 0·01 N potassium hydroxide in sealed ampoules at 100° C. for several hours, the maximum at 276 mμ disappeared and was replaced by the maximum at 408 mμ due to the alkaline form of *p*-nitrophenol. Experiments on the analysis of viscera showed that a clean extraction of parathion could be made with *n*-hexane as solvent, the parathion present being determined spectrophotometrically, using the peak at 276 mμ; hydrolysis to *p*-nitrophenol and measurement of the light absorption at 408 mμ gave an added identification and check on the concentration present. R. E. S.

Zinc in Copper Sulphate, Detection of. M. Langejan and J. A. C. van Pinxteren. (*Pharm. Weekbl.*, 1955, **90**, 333.) Two new methods are given for the detection of small quantities of zinc in copper sulphate. By the first, 100 mg. of copper sulphate is dissolved in 10 ml. of hot water, treated with 2 ml. of 4 N sodium hydroxide solution, and boiled. After cooling and filtering, the filtrate is acidified with acetic acid and 2 drops of potassium ferrocyanide solution are added. After 30 minutes the solution should not be turbid. This method will detect 0·25 mg. of zinc sulphate. In the second method, 100 mg. of copper sulphate dissolved in 1 ml. of water is treated with 0·25 ml. of dilute acetic acid and 300 mg. of sheet aluminium. The mixture is heated on the water bath for 5 minutes. The solution is decanted, treated with 1 drop of hydrogen peroxide (3 per cent.), and brought to the boil. After cooling, 3 drops of ammonium mercurithiocyanate solution and 1 drop of phosphoric acid is added. After rubbing with a glass rod a precipitate results which may be greenish yellow, but not violet or dark coloured. This test will detect 0·1 to 0·2 per cent. of zinc sulphate. G. M.

BIOCHEMISTRY

GENERAL BIOCHEMISTRY

Prothrombin and the One-stage Prothrombin Time. A. J. Quick and C. V. Hussey. (*Brit. med. J.*, 1955, **1**, 934.) Two accessory factors are known to affect the prothrombin time as determined in the one-stage test and the authors report experimental and clinical observations on the effects of these factors in relation to a re-evaluation of the test. One factor (the "labile factor") disappears from human plasma during storage; the second factor is distinguished as the "stable factor". The blood used in the investigation was obtained from 3 patients with hypoprothrombinæmia, each having a normal concentration of labile factor and a prolonged prothrombin time not shortened by adding stable factor. A further patient having a prothrombin time varying from 26 to 55 seconds, due to stable factor deficiency, was also used. By determining the effect of adding one or other of the two factors to normal and deficient plasma, it was shown that the constancy of the prothrombin time of normal fresh plasma can be explained by assuming constancy in the prothrombin level. Experiments on stored plasma showed that changes in the prothrombin time of stored blood are due to loss of labile factor and to either an increase of the prothrombin content or to generation of an accelerator independent of the two known accessory factors. The prothrombin time of serum from hæmophilic or thrombocytopenic blood is shorter than that from the corresponding plasma because almost no prothrombin is consumed and in addition either more prothrombin is formed or an accelerator is generated. The prothrombin content of the blood of newborn infants is only about 30 per cent. of that of adults but the normal prothrombin time is the same, namely 12 seconds. It has been shown that both accessory factors are deficient in newborn infants. The authors find that the prothrombin time of the plasma of newborn infants does not decrease on storage and that the time for the serum from platelet-poor newborn plasma is the same as that of the original plasma but higher than that for serum from platelet-poor adult plasma. The authors suggest that their observations can be explained on the hypothesis that adult blood, but not newborn blood, contains a prothrombin precursor, "prothrombinogen", kept inactive by an inhibitor. On storage or clotting, the inhibitor disappears and prothrombin is liberated. The one-stage prothrombin test measures active prothrombin whereas the two-stage method includes also the prothrombinogen. As the two methods measure different things, one cannot be used to assess the reliability of the other. The one-stage method remains the simplest and most reliable method of determining prothrombin. H. T. B.

BIOCHEMICAL ANALYSIS

***p*-Aminosalicylic Acid and Isoniazid Blood Levels, Determinations of, with Vanillin.** E. N. Deeb and G. R. Vitagliano. (*J. Amer. pharm. Ass., Sci. Ed.*, 1955, **44**, 182.) A simple method depends on the formation of yellow compounds by reaction with vanillin. The following method is recommended for the determination of *p*-aminosalicylic acid. To 2 ml. of plasma add water to produce 12 ml. followed by 4 ml. of a 20 per cent. solution of trichloroacetic acid. Centrifuge, filter and to 8 ml. of clear filtrate add 1 ml. of 10 per cent. solution of vanillin in ethanol (50 per cent.). Allow to stand for 10 minutes and determine the light absorption at 410 mμ. The result is calculated by comparison with the light absorption of solutions prepared by adding known quantities of *p*-aminosalicylic acid to normal plasma and treating as above. A

similar procedure may be employed for the determination of isoniazid, using 4-ml. samples of plasma and a 2 per cent. solution of vanillin in N sulphuric acid, the absorption measurements being carried out at 400 mμ. The precision of the method is ±0·9 per cent. for *p*-aminosalicylic acid and ±0·4 per cent. for isoniazid. G. B.

Boric Acid in Biological Materials, Determination of. W. C. Smith, A. J. Goudie and J. N. Sivertson. (*Analyt. Chem.*, 1955, **27**, 295.) The determination of traces of boric acid in blood, urine and animal tissues is accomplished by a colorimetric method using carminic acid. Organic matter is destroyed by fusing the sample with lithium carbonate and dissolving the residue in hydrochloric acid. Sulphuric acid is then added followed by a solution of carminic acid; the resulting colour is measured spectrophotometrically at 575 mμ after 5 minutes. Both carmine N.F. and carminic acid produced the colour satisfactorily but the colour developed much more rapidly with carminic acid. Inorganic materials that are normally found in blood, urine, and animal tissue did not interfere appreciably. The method was applied satisfactorily to the determination of boron in blood, urine, lung, heart, thymus, liver, spleen, stomach, duodenum, kidney, prostate or uterus, brain, voluntary muscle, skin, urinary bladder, jejunum, cæcum, and terminal colon, as well as fæcal matter and gastric contents. R. E. S.

Calcium in Serum, Estimation of. S. Natelson and R. Penniall. (*Analyt. Chem.*, 1955, **27**, 434.) A colorimetric method is described for the determination of calcium by extraction of the calcium-alizarin complex in *n*-octanol. Practical or technical grades of triethanolamine are used to adjust the *p*H to avoid turbidity in the alcohol phase; pure grades of triethanolamine were unsatisfactory. The serum sample (fresh) is diluted with water, and aqueous triethanolamine and alizarin solution in *n*-octanol are added from burettes. After shaking for 20 minutes the mixture is centrifuged and the colour is measured absorptiometrically at 560 mμ after dilution with *n*-octanol. Using inorganic alkali, iron interferes; a number of satisfactory grades of triethanolamine are listed. For human serum a factor of 7 per cent. for magnesium interference has to be deducted. When relatively large amounts of serum are available it is preferable first to precipitate the calcium as oxalate. R. E. S.

Iron in Plasma, Determination of. T. H. Bothwell and B. Mallett. (*Biochem. J.*, 1955, **59**, 599.) A method is presented for the determination of iron in plasma or serum in which hydrochloric acid is added to the sample and the plasma proteins are precipitated with trichloroacetic acid. After centrifuging, the supernatant fluid is decanted and is added to a mixture of thioglycollic acid, 2:2′-dipyridyl (in glacial acetic acid) and a saturated solution of sodium acetate. The mixture is shaken and the colour intensity is measured absorptiometrically, the concentration of iron being obtained by comparison with a standard curve prepared using known amounts of iron; a reagent blank is also measured. A table is given showing that complete recoveries were obtained in 101 estimations. By giving tracer doses of ^{59}Fe parenterally or orally, radioactive plasma samples with the transport iron attached to β_1-globulin were obtained; this iron was found to be completely separated from its protein attachment after thorough mixing with dilute hydrochloric and trichloroacetic acids. R. E. S,

Salicylic Acid and Two Metabolites in Plasma and Urine, Determination of, using Fluorimetry. E. B. Truitt, Jr., A. M. Morgan and J. M. Little. (*J. Amer. pharm. Ass., Sci. Ed.*, 1955, **44**, 142.) Determinations of free salicylic acid in plasma and urine were carried out by extraction with carbon tetrachloride, followed by measurement of the colour produced by reaction with ferric nitrate. On account of the relatively high solubility of salicylic acid in the solvent, and the weak colour produced by salicyluric acid, the test was 50 times more sensitive to salicylic than salicyluric acid and corrections were necessary only when large quantities of the latter were present, for example in human urine. Salicyluric acid was determined by extraction of plasma or urine with ethylene dichloride and measurement of the fluorescence at *p*H 10. Salicylic acid gave a relatively weak fluorescence under these conditions but a small correction was usually necessary. The quantity of salicylglycuronides was estimated by submitting diluted urine samples to hydrolysis with concentrated hydrochloric acid in a boiling water bath for 3 hours, during which time the whole of the salicylglycuronides and 62 per cent. of the salicyluric acid were hydrolysed to salicylic acid. The solution was extracted with ethylene dichloride and total salicylate determined by the ferric nitrate method. A reference curve was made using urine containing known quantities of salicylic acid treated under the same conditions, since hydrochloric acid affects the efficiency of the extraction procedure. A synthetic sample of *O*-(β-D-glucuronosido)salicylic acid gave no colour with ferric nitrate until hydrolysed with hydrochloric acid and did not contribute to the fluorescence of ethylene dichloride extracts. G. B.

CHEMOTHERAPY

***N*-(2-Hydroxy-5-chlorobenzylidine)anilines and *N*-(2-Hydroxy-5-chlorobenzyl) anilines.** D. B. Reisner and P. M. Borick. (*J. Amer. pharm. Ass., Sci. Ed.*, 1955, **44**, 148.) A number of *N*-(2-hydroxy-5-chlorobenzylidine)anilines were prepared by reaction of 5-chlorosalicylaldehyde with the required aromatic amine in alcoholic solution. The corresponding *N*-(2-hydroxy-5-chlorobenzyl) anilines were prepared by catalytic reduction of the corresponding Schiff's bases in the presence of platinum oxide and acetic acid. Compounds of both series were tested for bacteriostatic and fungistatic activity against *Escherichia coli*, *Micrococcus pyogenes* var. *aureus*, *Trichophyton interdigitale*, *Mycophyton audouini* and *Candida albicans* by a serial dilution method. The compounds showed a high degree of activity, the most active substances studied being the *N*-(2-hydroxy-5-chlorobenzyl)chloroanilines and *N*-(2-hydroxy-5-chlorobenzyl) 1-naphthylamine. G. B.

***iso*Nicotinoylsalicylidene Hydrazine as a Tuberculostatic.** T. Cänback, N. Diding, P. Lundgren, P. Ekeblad, O. Alm, K. Erne and S. Linde. (*Svensk farm. Tidskr.*, 1955, **24**, 1.) Tests are reported on the nicotinylhydrazide of salicylic aldehyde ("Acozide"). Compared with isoniazid in tests *in vitro* on *Myco. tuberculosis*, its activity is only about one tenth. On the other hand, the subcutaneous toxicity of the new compound is less than one twentieth of that of isoniazid, while comparison of oral toxicities is even more favourable. Acozide may be determined photometrically by measuring the extinction at 288 mμ at *p*H 6. The shape of the extinction curve alters with the *p*H. In presence of isoniazid or salicylaldehyde (hydrolysis products) it is necessary to make measurements also at 251, 255·5 or 262 mμ, and to compare the figures with that at 288 mμ. G. M.

PHARMACY

NOTES AND FORMULÆ

Antacids, A Study of. J. K. Dale and R. E. Booth. (*J. Amer. pharm. Ass., Sci. Ed.*, 1955, **44**, 170.) A series of ingredients of antacid mixtures, some experimental formulæ and 24 commercial products were examined, two tests being employed. Either the *p*H was determined after the addition of varying amounts of antacid to 100 ml. of 0·1N hydrochloric acid, or 1 dose of antacid was added to 50 ml. of 0·1N hydrochloric acid, 2 ml. of N hydrochloric acid being added every 10 minutes and the *p*H determined at intervals. Mixtures of aluminium hydroxide and magnesium trisilicate were the best antacids at *p*H 4 or below, whereas a mixture of 12 parts of calcium carbonate, 2 of magnesium trisilicate and 1 of magnesium carbonate was better below *p*H 6·8. For the Sippy treatment, requiring neutralisation to *p*H 7 or below, a mixture of equal quantities of magnesium carbonate and sodium bicarbonate was most effective. In these experiments bentonite, kaolin, aluminium silicate, silica gel, sodium cellulose sulphate, veegum, methylcellulose and guar gum had no buffering action. Only slight buffering action was obtained with sodium carboxymethylcellulose, bismuth subcarbonate, calcium gluconate and calcium glycerophosphate. Effective buffers were prepared from aluminium phosphate, bone phosphates, glycine, polyamine methylene resin, calcium citrate, dicalcium phosphate, aluminium hydroxide, magnesium trisilicate, colloidal magnesium silicate, calcium carbonate, sodium bicarbonate, magnesium carbonate and magnesium oxide. Variations in buffering power were observed in examining samples of pharmacopœial quality and it is suggested that further tests should be added to the monographs. G. B.

Cycrimine Hydrochloride (Pagitane Hydrochloride). (*New and Nonofficial Remedies*; *J. Amer. med. Ass.*, 1955, **157**, 510.) Cycrimine hydrochloride is *cyclo*pentylphenyl-3-(1-piperidyl)-1-propanol hydrochloride and occurs as a white, odourless, bitter substance, m. pt. 241° to 244° C. (with decomposition), soluble, at 25° C., in 150 parts of water, in 50 parts of ethanol, and 33 parts of chloroform, and practically insoluble in benzene and ether. A 0·5 per cent. solution in water has *p*H 4·9 to 5·4, and when made alkaline with sodium hydroxide and cooled overnight yields a precipitate of cycrimine, which melts at 90° to 96° C., after washing with a little cold water and drying in a vacuum over phosphorus pentoxide for 5 hours. A 0·07 per cent. solution in water exhibits ultra-violet absorption maxima at about 251, 257 and 263 mμ ($E^{1\ per\ cent.}_{1\ cm.}$, about 5·4, 6·2 and 5·0), minima at about 230, 254 and 261 mμ, and an inflection point at about 247 mμ. The ratio of the absorptions at 251 and 257 mμ is 1·0 to 1·3. Cycrimine hydrochloride loses not more than 1·0 per cent. of its weight when dried at 105° C. for 5 hours, and yields not more than 0·1 per cent. of sulphated ash; the limit of heavy metals is 20 parts per million. It is assayed in solution in glacial acetic acid, by the addition of a 6 per cent. solution of mercuric acetate and titration with 0·1 N perchloric acid, using crystal violet as indicator; it contains 97 to 103 per cent. of cycrimine hydrochloride. Tablets are identified by extracting with chloroform and applying the identity tests for chloride and melting point of the free base to the residue obtained on evaporation. They contain 92·5 to 107·5 per cent. of the labelled amount of cycrimine hydrochloride, and are assayed by extracting the base from an alkaline solution with ether, extracting the ether with sulphuric acid,

and titrating the excess of acid with sodium hydroxide, using methyl red as indicator. Cycrimine hydrochloride is used in the treatment of paralysis agitans. G. R. K.

Dihydrostreptomycin, Stability of Aqueous Solutions of. H. Vogt. (*Arch. Pharm. Berl.*, 1955, **288**, 26.) Aqueous solutions of dihydrostreptomycin sulphate lose 8 to 9 per cent. of their activity after 6 weeks in a refrigerator, and 11 to 12 per cent. at room temperature. If the solutions are first sterilised at 120° C. then the losses are about 15 per cent. in both cases. A buffered solution (pH = 3·6) only decomposes to about one half the extent of an unbuffered one. Ointments containing dihydrostreptomycin with yellow soft paraffin lose strength at about the same rate as the aqueous solutions, i.e., about 11 to 12 per cent. after 5 weeks. Thus the stability of dihydrostreptomycin is appreciably greater than that of penicillin. G. M.

Pyrogens, Testing Injections for. A. Engelund and P. Terp. (*Arch. pharm. chemi*, 1955, **62**, 1.) In testing for pyrogens, the injection of 10 ml. of a solution into a rabbit may sometimes result in toxic effects. This applies to a 10 per cent. solution of calcium gluconate, and in this case it is recommended that 10 ml. of a 2 per cent. solution should be used for the test. The method of precipitating the calcium with sodium carbonate before injection is not advised. For a 2 per cent. solution of sodium citrate, it is necessary either to dilute with water or saline to a concentration of 1 per cent., of which 10 ml. is injected; or calcium equivalent to the citrate must be added. Injections containing potassium may be injected without trouble. G. M.

PHARMACOGNOSY

Alkaloidal Ontogenesis in *Lupinus luteus*. A. van der Kuy. (*Pharm. Weekbl.*, 1955, **90**, 65.) The three chief alkaloids of *Lupinus luteus* may be precipitated by flavianic acid in ether solution. Lupinine flavianate is separated by precipitation in chloroform, in which the flavianates of the other two are insoluble. Sparteine and lupanine are easily separated, since only the former is volatile in steam. Studies on the plant at different stages showed the following picture. Lupinine is the chief alkaloid of the seed, but disappears soon after germination, reappearing during flowering and fruiting. It is never found in the root. Sparteine is a major constituent at all times and in all organs. In addition to sparteine and lupinine, other alkaloids are present in all vegetative parts of the plant. At certain stages these are present in greater amount than sparteine. G. M.

***Datura* Species, Hybridisation Experiments with.** E. Steinegger. (*Pharm. Acta Helvet.*, 1954, **29**, 378.) Hybridisation of *D. stramonium* (tetraploid). *D. tatula* and *D. tatula* var. inermis generally gives satisfactory results, but attempts to cross *D. innoxia* with the above species were unsuccessful, since very few of the seeds could be germinated. Certain abnormalities were observed on 4n mother plants: fruit formation without seeds; fruit with very small seeds which would not germinate; fruit with seeds producing diploid offspring similar to the mother plant but with lower chromosome number; and tetraploid offspring identical with the mother plants. The 4n offspring showed no alteration in alkaloidal content, whereas the 2n offspring from 4n mother plants had a considerably reduced alkaloidal content. This is a confirmation of the effect of polyploidy in increasing the content. G. M.

***Rheum palmatum*, Anthraglycoside Content of.** E. Schratz and H. Tombergs. (*Arzneimitt.-Forsch.*, 1954, **4**, 678.) For the assay of rhubarb root, free anthraquinones are determined by extraction of the root with anhydrous ether, the ethereal solution being then shaken out with a solution containing 5 per cent. of sodium hydroxide and 2 per cent. of ammonia. The extinction is then measured. For combined anthraquinones and reduced antharacene derivatives, 50 mg. is refluxed with 7·5 ml. of glacial acetic acid, then exhausted with ether. The solution is neutralised with soda (taking care to avoid any rise of temperature), and the anthraquinone fraction is shaken out into the above alkaline solution. It is then determined photometrically, using pure 1:8-dihydroxyanthraquinone as standard. The content of reduced anthraquinone compounds is determined similarly after oxidation by heating for two hours on the water bath. It is not possible to avoid a certain amount of oxidation of the anthranols during the alkaline treatment, and for this reason it is essential to cool the acid mixture during neutralisation, and to cut down the time of exposure to alkali to a minimum. The colorimetric determinations should be carried out as soon as possible. Mean results of a large number of determinations are summarised in the tables below (calculated as percentage of dry weight of the root).

Total content		Anthranol content		Anthraquinone content	
Summer	Winter	Summer	Winter	Summer	Winter
3·09	3·01	1·10	1·165	2·02	1·76

Percentage of total content:			
Anthranols		Free anthraquinones	
Summer	Winter	Summer	Winter
35·1	34·8	26·7	34·1

These tests were carried out on about 300 individual plants of *Rheum palmatum*. The total content of anthracene derivatives varied greatly: the range of variation being from about 1·5 to 6·0 per cent. No significant difference could be detected between the plants at the height of the vegetative period (August) and at mid-winter (December). G. M.

PHARMACOLOGY AND THERAPEUTICS

Adrenaline and Noradrenaline, Potentiation of, by Local Anæsthetics. H. E. D'Amato and A. P. Truant. (*Arch. int. Pharmacodyn.*, 1955, **100**, 113.) In the unanæsthetised dog local anæsthetics—procaine, lidocaine, butethamine, metabutethamine and pravocaine—potentiate, like cocaine, the pressor response to adrenaline. Diastolic pressure is potentiated to a greater extent than systolic pressure. Anæsthetised dogs do not always show the potentiation, depth of anæsthesia and type of anæsthetic affecting the response. Potentiation with synthetic local anæsthetics, unlike cocaine which may last for over an hour, is relatively short lived. Atropinisation, ganglionic or adrenolytic blockade do not abolish or diminish potentiation by cocaine or procaine. The depressor response to small doses of adrenaline is converted to a pressor response by cocaine and the depressor response after adrenergic blockade is also potentiated. The pressor response of noradrenaline is also potentiated and there is a greater degree of potentiation of noradrenaline than adrenaline with cocaine. Local anæsthetics do not modify the pressor response to occlusion of the carotid arteries.

G. F. S.

Alkyl Tin Compounds, Studies on the Toxicity of. H. B. Stoner, J. M. Barnes and J. I. Duff. (*Brit. J. Pharmacol.*, 1955, **10**, 16.) A series of mono-, di-, tri and tetra- alkyl tin compounds and some other organic tin compounds were studied in rats, rabbits, guinea-pigs and fowls. In acute experiments on rabbits, triethyl tin, the most active compound, produced muscular weakness, followed by an apparent partial recovery and then by muscular tremors, which led to convulsions and death. This general pattern was common to all of the compounds and species studied, with slight variation. Other actions observed were vasodilatation of the blood vessels of the rabbits' ear, fall in rectal temperature in the rat and rabbit, a vasopressor action in the cat and neuromuscular blockade in the rabbit and rat. Chronic administration of the tin compounds caused in all species muscular weakness. The main site of action appeared to be the central nervous system, although there was no evidence of concentration of the compounds in any particular organ. In the case of diethyl tin, the mode of action may involve reaction with sulphhydryl groups as its toxic effects were antagonized by dimercaprol. Dimercaprol had no effect on the toxicity of triethyl tin. The effects of tetraethyl tin resembled those of triethyl tin closely after an initial latent period, which suggests *in vivo* conversion of the tetra- to the tri-alkyl derivative. Since the delayed effects of triethyl tin poisoning could be reproduced by large doses of sodium tin tartrate, the same relationship might exist between triethyl tin and other forms of tin, as exists between lead, mercury and antimony and their respective alkyl derivatives. G. P.

Anthelmintic Activity, *In Vitro* Tests for, on *Ascaris lumbricoides* and *Fasciola hepatica*. A. Mackie, G. M. Stewart, A. A. Cutler and A. L. Misra. (*Brit. J. Pharmacol.*, 1955, **10**, 7.) The anthelminthic activity of derivatives of 2:3-dihydro-3-ketobenzo-1:4-thiazine, phenothiazine and rhodanine, and of other miscellaneous compounds against *Fasciola hepatica* (liver fluke), and the anterior preparation of *Ascaris lumbricoides* ("roundworm"), was assessed *in vitro* by kymographic technique. The 2:3-dihydro-3-ketobenzo-1:4-thiazine derivatives, where active, showed only depressant effects against *A. lumbricoides*, although some activity against the liver fluke was observed in some of these compounds, particularly the 6-bromo compound. Increase in side-chain length usually decreased the activity against the liver fluke. Some of the amino-acetylphenothiazines were active against the liver fluke; β-10-phenothiazinyl propionic acid was lethal. Of the rhodanine derivatives, only 5-*iso*nitroso-3-allyl-rhodanine paralysed *Ascaris*, but some, especially the benzylidene compounds killed the liver fluke. Among the miscellaneous compounds the following were very active: allyl iodide and sodium azide, against *Ascaris*; carbon tetrabromide, benzene hexachloride, allyl iodide, allyl *iso*thiocyanate, mercuric chloride, ethyl mercuric chloride, ethoxyethyl mercuric chloride, diphenylamine and *p*-nitrophenol, against *Fasciola*. G. P.

Chlorpromazine, Effect of Temperature on the Toxicity of. T. Berti and L. Cima. (*Arzneimitt.-Forsch.*, 1955, **5**, 73.) The influence of temperature on the toxicity or chlorpromazine to mice was investigated. The effect of temperature is very marked. Doses of 100 mg./kg., which are certainly fatal at 18 to 20° C. and also at 33 to 38° C., do not kill at 28 to 29° C. The toxicity between 25·5 and 30·5° C. is 30 times less than that at lower temperatures. At the lower temperatures the predominant symptoms are of central depression; as the temperature rises excitation symptoms become more clearly marked. At 30° C. death occurs from violent convulsions. G. M.

Cholinesterase Inhibition and Increase in Muscle Tone in Rabbit Duodenum, a Correlation Between. H. Shelley. (*Brit. J. Pharmacol.*, 1955, **10**, 26.) The increase in tone caused by eserine and dyflos in isolated strips of longitudinal muscle from rabbit duodenum and in the isolated intact duodenum was closely correlated with the inhibition by these drugs of the true cholinesterase in the two tissues. Increase in tone first appeared with eserine concentration of $2{\cdot}7 \times 10^{-8}$ M or with dyflos concentration of 10^{-7} M. As the anticholinesterase concentration was increased, tone also increased to a maximum with $2{\cdot}7 \times 10^{-6}$ M eserine or 10^{-5} M dyflos. Above these concentrations tone decreased. The distribution of true- and pseudo- cholinesterases in the different layers of the duodenum was determined manometrically. Highest activity of both enzymes was found in the longitudinal muscle layer, to which most of the cells and fibres of Auerbach's plexus were found to adhere on separation. The true- and pseudo- cholinesterases of these longitudinal muscle strips were equally inhibited by eserine, but with dyflos the pseudocholinesterase was much more readily inhibited. In estimating the degree of inhibition of the enzymes in the longitudinal muscle strips the muscle was treated with dyflos and then homogenized. This procedure gave results similar to that where the muscle was homogenized before treatment with the dyflos, showing adequate penetration of the dyflos into the tissue. G. P.

Compound 48/80, the Effect of, on Ganglionic Transmission. S. B. Gertner. (*Brit. J. Pharmacol.*, 1955, **10**, 103.) Both compound 48/80 and propamidine blocked transmission through the cat superior cervical ganglion, perfused with Locke solution, contraction of the nictitating membrane being used as an indication of transmission. Injected into the ganglionic circulation 48/80 had no ganglion-stimulating action in doses up to 100 μg., but regularly produced relaxation of the nictitating membrane during continuous preganglionic stimulation. Acetylcholine release during ganglion block by 48/80 was estimated on the eserinised dorsal muscle of the leech and did not differ from ACh release during normal transmission. The sensitivity of the ganglion to stimulation by injected ACh was decreased by 48/80; the block could be overcome partially by increasing the dose of ACh. The release of histamine from the ganglion could not account for the block by 48/80 since; (*a*) ganglionic transmission is not impaired by histamine; (*b*) the degree of block is not increased by histamine; (*c*) the amounts of histamine released decreased with successive injections of 48/80 whereas the block became more pronounced, so that even when no histamine was being liberated block was still obtained. This effect could explain the finding that in rats depleted of their tissue histamine by repeated injections of 48/80 there was still a residual vasodepressor effect with subsequent injections of the liberator (Nasmyth, *Brit. J. Pharmacol.*, 1955, **10**, 51). (*see* p. 618). G. P.

β-Diethylaminoethyl Diphenylpropylacetate Hydrochloride, Enhancement of the Action of Analgesic Drugs by. L. Cook, G. Navis and E. J. Fellows. (*J. Pharmacol.*, 1954, **112**, 473.) In the rat, β-diethylaminoethyl diphenylpropylacetate hydrochloride (SKF525-A) prolonged the analgesic action of morphine, methadone, pethidine, codeine and methorphinan. The LD50 estimates of morphine and pethidine were not significantly altered nor was the respiratory depressant action of morphine increased by the drug. In rats tolerant to morphine, SKF525-A increased the effects of further doses of the analgesic; however, tolerance was just as easily induced by morphine–SKF525-A combinations as with morphine alone. SKF525-A, alone, had a slight analgesic effect, but only in doses much larger than those used to potentiate the analgesics. G. P.

Ferritin, Study of the Pharmacology of. T. J. Haley and J. L. Leitch. (*Arch. int. Pharmacodyn.*, 1954, **100**, 120.) Ferritin is the form in which iron is transported from the intestine and stored in the liver. Ferritin extracted from dog liver, spleen and horse spleen is shown to have little effect on the isolated guinea-pig heart, on the pressor and respiratory effects of adrenaline in the rabbit, cat or dog and on the response of the cat nictitating membrane to adrenaline and to preganglionic stimulation. It also did not alter the blood flow in the hind limb of the dog or the response of the isolated guinea-pig seminal vesicle to adrenaline. G. F. S.

Heterocyclic Bis-quaternary Compounds, Particularly of a Pyrrolidinium Series, the Actions of. D. F. J. Mason and R. Wien. (*Brit. J. Pharmacol.*, 1955, **10**, 124.) The actions of three series of bis-quaternary salts having the general formula $A.(CH_2)_n.A$, where A is a heterocyclic nucleus (1-methylpiperidino-, 4-methylmorpholino-, or 1-methylpyrrolidino-) were studied on transmission through the superior cervical, vagal and ciliary ganglia of the cat, on salivary flow in the cat, on the peristaltic reflex of the guinea-pig ileum and on neuromuscular transmission in the cat and rabbit. Anticholinesterase activity was measured manometrically on horse erythrocyte cholinesterase. Where the quaternizing groups on the nitrogen atoms were methyl, compounds of the piperidinium series where $n = 4$, 5 and 6 and of the morpholinium series where $n = 5$ and 6, all had ganglion-blocking activity similar to that of hexamethonium. In the piperidinium series the decane members (and where the quaternizing groups were either methyl or ethyl) had about one-fifth the activity of tubocurarine at the neuromuscular junction, but the morpholinium series had negligible activity at this site. The pentane member of the pyrrolidinium series (with methyl quaternizing groups) had peak ganglion-blocking activity of all the compounds and was about five times as active as hexamethonium on the superior cervical ganglion of the cat. The mode of action of this compound, called "pentapyrrolidinium" [pentamethylene-1 : 5 bis-(1-methyl-pyrrolidinium)] was similar to that of hexamethonium. G. P.

Histamine Release and the "Stress" Phenomenon. P. A. Nasmyth. (*Brit. J. Pharmacol.*, 1955, **10**, 51.) The histamine-liberator 48/80 precipitated the stress phenomenon on subcutaneous injection into normal rats, in a dose of 0·5 mg./100 g. body weight. At this dose level there was a marked depletion of the adrenal ascorbic acid content. In rats where the tissue histamine had previously been depleted by 48/80 administration, a further 0·5 mg./100 g. of the liberator had less action on the adrenal ascorbic acid than in the normal animal. Where the adrenals had been demedullated 36 to 56 days previously the ascorbic acid depletion was more prolonged than in the normal animal, after 48/80 administration, but where six months had elapsed between operation and 48/80 administration there was no significant difference between operated and normal. The reason for this may be that the adrenal cortical tissue had not regenerated adequately within 36 to 56 days of the operation. 0·5 mg./kg. of 48/80 injected intravenously had much less effect on the blood pressure of the histamine-depleted than on the normal rats, due to a decreased release of histamine. It was not possible to say how far this accounted for the reduced effect on the adrenal ascorbic acid in these animals. In demedullated rats the blood pressure after intravenous injection of 48/80 followed the same pattern as in the normal and histamine-depleted animals, but the fall was more precipitous and death invariably occurred between 20 and 30 minutes after the dose. It was concluded that released histamine plays some part in the response of the adrenal cortex to 48/80. G. P.

Histamine Release in Rabbit Blood by Dextran and Dextran Sulphate. C. G. Haining. (*Brit. J. Pharmacol.*, 1955, **10**, 87.) The cellular histamine of rabbit blood is known to be released by a number of compounds causing anaphylaxis and anaphylactoid reactions *in vivo*. Dextran and dextran sulphate, which produce these reactions in the rat, guinea-pig and man, were also found to cause histamine release on incubation with rabbit blood for 30 minutes at 37° C. The liberated histamine was extracted and assayed on the guinea-pig ileum. Histamine release by dextran depended upon the concentration and molecular weight, samples of mol. wt. between 22,000 and 1,000,000 being effective, but not those below 14,000. Similarly, with dextran sulphate, samples of mol. wt. below 10,000 were inactive, the effect being graded for samples between 40,000 and 440,000. Dextran sulphate differed from dextran in that there was an optimum concentration necessary for maximum histamine release. Dextran sulphate of high mol. wt. had a dual action, behaving as an activator of the histamine release mechanism at low concentrations and as an inhibitor at high concentrations. Histamine release by the dextran sulphate of mol. wt. 440,000 was inhibited by sodium oxalate, heparin, maltotriose sulphate and low mol. wt. dextran sulphate. Low mol. wt. dextran was ineffective as an inhibitor, suggesting the importance of the sulphate ester group. G. P.

5-Hydroxytryptamine, Effects of, on the Nictitating Membrane of the Cat. J. Lecomte. (*Arch. int. Pharmacodyn.*, 1955, **100**, 457.) The actions of intravenous and intra-arterial injections of 5-hydroxytryptamine in conjunction with serotonin and antihistamine compounds have been studied on the blood pressure and nictitating membrane of the anæsthetised cat. 5-Hydroxytryptamine had a direct contracting action on the nictitating membrane which was potentiated by the local instillation of tutocaine. The response was related to the dose but tachyphylaxis occurred. The response of the nictitating membrane to adrenaline was potentiated. Intra-arterial injections into the aorta, close to the suprarenal arteries, caused a smaller and slower contraction. Administration of 10 to 30 mg./kg. of mepyramine intravenously increased the contractions of the nictitating membrane to intravenous injections of adrenaline and serotonin, but abolished the response to intra-arterial injections of serotonin. Promethazine, 17·5 mg. per kg. abolished the contractions to adrenaline and serotonin. Local instillation of a 1 per cent. solution of chlorpromazine also abolished the responses. G. F. S.

Mephenesin, the Effect of, on Barbiturate Anæsthesia. F. M. Berger and T. E. Lynes. (*Arch. int. Pharmacodyn.*, 1955, **100**, 401.) Experiments carried out in mice show that mephenesin has a synergistic action with hexobarbitone and butabarbital and that mephenesin suppresses prehypnotic excitement. The combined action of mephenesin and pentobarbitone is merely additive, but the combined effect of butabarbital and mephenesin varies with the experimental design from incomplete addition to potentiation. It is suggested that the modifying effect of mephenesin on barbiturate anæsthesia will be of considerable value in therapeutics. G. F. S.

Meratran, New Blocking Agent against LSD 25 Psychosis. H. D. Fabing. (*Science*, 1955, **121**, 208.) Meratran (α-(4-piperidyl) benzhydrol hydrochloride) blocked the psychotic states precipitated in normal healthy subjects by the oral administration of 100 μg. of lysergic acid diethylamide (LSD25). The visceral effects of LSD25 (nausea, dryness of the mouth, sweating and numbness in the limbs) were unaffected. Blockade of the psychosis was achieved either by an

oral dose schedule before ingestion of the LSD25 or by intravenous injection during the psychosis. The blocking agent alone produced no subjective or objective reactions during the premedication period. Preliminary experiments with mescaline sulphate suggest that the psychosis induced with this drug is also abolished by the blocking agent. G. P.

***N*-(4-Methoxybenzyl)-*iso*quinolinium Chloride, Pharmacology of.** J. Dipalma. (*J. Pharmacol.*, 1955, **113**, 125.) This drug is an aromatic quarternary ammonium compound. Its main action is to increase the rate and force of the heart beat. This has been shown on the isolated atrium of the cat, in intact dogs and in humans. It is more potent than quinidine in raising the threshold of electrically induced atrial fibrillation in the cat, but is unlike quinidine in that it does not protect against adrenaline-hydrocarbon induced arrhythmias. It has weak ganglionic and neuromuscular blocking actions. It also causes local anæsthesia when injected intradermally, having the same order of potency as procaine. The drug is well tolerated in man in doses up to 5 mg./kg., the only side-effects being a transient dilation of the pupils, flushing and occasionally vertigo. It is now undergoing clinical trial. M. M.

Myleran in Chronic Myeloid Leukæmia. D. A. G. Galton and M. Till. (*Lancet*, 1955, **268**, 425.) Of 11 patients suffering from chronic myeloid leukæmia treated with myleran alone for periods varying from 1 to 4 years, 7 are still living; only 2 have been observed for more than 3 years from diagnosis which is about the median survival from diagnosis in patients treated by external radiation and with radioactive phosphorus. It is therefore too early to compare the survival-rates of patients treated with myleran alone with those treated by radiotherapy alone. Thus, while myleran cannot at present be advocated as a first line of treatment, it appears to be a satisfactory substitute for radiotherapy and can justifiably be used as such if radiotherapy is unavailable, impracticable or contra-indicated. Administration was by means of tablets containing 0·5 or 2 mg., the standard dose for an adult being 0·06 mg./kg. of bodyweight daily (about 4 mg.). Treatment was stopped when the clinical and hæmatological improvement seemed to justify it or when the leucocyte count was thought to be falling too steeply. With the daily standard dosage the treatment lasted from 3 to 7 months. Subsequent treatment was deferred until symptoms returned; symptoms reappeared in from 5 to 18 months. Remissions following second and third courses of myleran were usually shorter, none exceeding 1 year. The dose required for maintenance varied considerably, the smallest dose used being 0·5 mg. daily and the largest 6 mg. daily. No patient has yet received continuous therapy for longer than 23 months, but the development of specific resistance to myleran in 3 patients suggests that it will not be effective indefinitely. The general response to myleran therapy, previously observed, was confirmed. Symptoms were rapidly relieved; the Hb level rose steadily; splenic regression, though somewhat slower than with radiotherapy, was equal in extent; and absolute and differential leucocyte counts approached normal. There were no side-effects, and thrombocytopenia, formerly thought to be an occasional hazard with therapeutic dosage, developed only once after avoidance of doses exceeding 0·06 mg./kg. of bodyweight daily. (Details are also included of 20 patients treated with myleran after previous courses of radiotherapy, radioactive phosphorus, urethane or nitrogen mustard.) S. L. W.

Nalorphine, the Effect of, on the Antidiuretic Action of Morphine in Rats and Man. H. Schnieden and E. K. Blackmore. (*Brit. J. Pharmacol.*, 1955, **10**, 45.) The antidiuretic effect of morphine injected subcutaneously into "water-loaded" rats was decreased by the simultaneous injection of a dose of nalorphine which alone had no antidiuretic action. The analgesic effects of morphine in rats were also reduced by nalorphine, which by itself had slight analgesic action. The antidiuretic effect of morphine in rats was partly due to a prolongation of gastric emptying time, and partly to a reduction in water excretion after it had been absorbed. Both effects were decreased by nalorphine. The water content of the brain of rats to which water had been administered was not significantly higher after morphine than after saline injection. In hydrated normal healthy men the marked antidiuretic effects of morphine were not affected by simultaneous injection of nalorphine. In some subjects nalorphine given alone produced an antidiuresis. G. P.

Phenobarbitone and Diphenylhydantoin Sodium, Anticonvulsant Properties of. G. Chen and C. R. Ensor. (*Arch. int. Pharmacodyn.*, 1954, **100**, 234.) The anticonvulsant properties of phenobarbitone, diphenylhydantoin sodium, pentobarbitone and barbitone and their combinations were investigated in mice by their depression of leptazol- and electroshock- induced convulsions. The anti-electroshock activity was greatest with phenobarbitone and diphenylhydantoin, being high at non-hypnotic dose levels, whereas both pentobarbitone and barbitone were only effective at minimal anæsthetic dosage. For both phenobarbitone and diphenylhydantoin the time course of action was the same, being slow to reach peak effect. In the combination of drugs it was found that pentobarbitone and barbitone were alike in their action, diphenylhydantoin and barbitone had different modes of action, but were additive, and with combinations of phenobarbitone and diphenylhydantoin there was a mutual potentiating effect. However, no potentiation beyond an additive effect was found for the LD 50 estimates in mice for phenobarbitone-diphenylhydantoin combinations. The anti-electroshock activity was suggested as a possible mechanism for the enhanced anti-epileptic efficacy of diphenylhydantoin-phenobarbitone mixtures. G. P.

Pitressin, Modifications in the Determination of the Antidiuretic Activity of. J. Tripod, C. Bruni and R. Meier. (*Arch. int. Pharmacodyn.*, 1955, **100**, 1.) For the determination of the antidiuretic activity of pitressin in the rat an initial water load of 50 ml./kg. by mouth gives the greatest sensitivity and is the simplest method for routine assays. Determination of the time of maximal excretion as described by Burn, or the determination of the urinary retention over 3 hours in relation to controls is a satisfactory and easy procedure. G. F. S.

Protoveratrine, Hypotensive Mechanism of. E. Fernandez and A. Cerletti. (*Arch. int. Pharmacodyn.*, 1955, **100**, 425.) In the intact cat, under chloralose-urethane anæsthesia, 1·5 to 2·5 μg. of protoveratrine causes a maximal fall in blood pressure of 26 per cent., which is reduced to 14 per cent. in the atropinised animal. After bilateral vagotomy the fall in blood pressure is very slow, a maximal effect taking 20 minutes. In animals with bilateral denervation of the carotid sinus, but with the vagus nerves intact, the blood pressure fall is more pronounced, and is reduced by prior administration of atropine. In vagotomised and carotid denervated cats protoveratrine has no hypotensive action, and in most cases the blood pressure increases. The results show that the vagus nerve plays the main role in the immediate hypotensive effect of protoveratrine and the carotid sinus has an important buffer action, diminishing the initial rapid

fall of blood pressure. A direct effect on the central nervous system does not play any important part in the hypotensive action of small doses of protoveratrine. G. F. S.

Quinoline Derivatives, Cardiovascular and Oxytocic Actions of a Series of. K. Kamijo and G. B. Koelle. (*J. Pharmacol.*, 1954, **112**, 444.) Three groups of quinoline derivatives were investigated for cardiovascular actions on the blood pressure of the dog and for oxytocic action on the isolated guinea-pig uterus and rabbit ileum. Group A, 3-quinolinecarboxamide derivatives had little activity of either type. Group B, tetrahydro-3-quinolinecarboxamides had slight hypotensive activity, but were relatively strong oxytocics. The mode of action appeared to differ from that of ergometrine. The 3-carbamylquinolinium halides (group C) were relatively strong hypotensive agents, but had no oxytocic activity. One member of this group, the most active, 1-methyl-3-[*N*-(1-carboethoxyethylcarbamyl)]quinolinium iodide, designated McN-259-15, was investigated in detail. Five mg./kg. intravenously in dogs caused a rapid, prolonged fall in blood pressure, accompanied by a brief tachycardia and apnœa. The hypotension lasted for from 30 minutes to 2 hours, but circulatory reflexes (response to carotid occlusion; stimulation of the central vagus) were depressed for longer periods. The initial rapid vasodepressor response appeared to be initiated from some structure in the head or neck, since intracarotid injections of small doses elicited this response and spinal cord section at C-3 effectively abolished it. Antihistamines had no effect on this initial action, but abolished the prolonged hypotension which followed. This prolonged phase appeared to be due to histamine liberation since it showed tachyphylaxis, considerable individual variation and was accompanied by increased peripheral blood flow. Ganglionic blockade, section of the vagi above or below the nodose ganglion, or spinal transection did not affect this response. Perfusion of the drug through the carotid sinus–carotid body circulation had no effect. The drug also did not inhibit cholinesterase, mono- or di-amine oxidase in pharmacological concentrations. Assays for histamine-like activity on the guinea-pig uterus showed an increased blood–histamine-equivalent during the hypotensive action of McN-259, which paralleled the degree of hypotension. Responses to McN-259 were considerably smaller in cats and rabbits than in dogs. The actions of the drug were discussed in comparison with those of other histamine liberators. G. P.

Reserpine in the Treatment of Hypertension. W. M. Hughes, E. Dennis and J. H. Moyer. (*Amer. J. med. Sci.*, 1955, **229**, 121.) This study was conducted on a group of 73 out-patients with mild to severe hypertension. Of this number, 26 received only reserpine, in a daily dose of 2 mg.; 6 of the patients so treated became normotensive. There was no evidence of tolerance to reserpine, and patients who were normotensive after 3 months of treatment have continued so for a year or more. In a further 15 patients, 14 of whom had previously been treated with reserpine alone without becoming normotensive, reserpine was used in combination with hydrallazine; 87 per cent. of the patients obtained a significant reduction in blood pressure on the combined therapy, and 33 per cent. became normotensive. The average daily dose of hydrallazine when combined with reserpine was 331 mg. in the responsive patients. In the remaining 32 patients, 27 of whom had failed to become normotensive under reserpine therapy alone, reserpine was used in combination with oral hexamethonium; 84 per cent. were responsive to the combined therapy and 47 per cent. became normotensive. The average daily dose of hexamethonium in

combination with reserpine for the responsive patients was 1·44 g. It was observed that the severity of side reactions of both hydrallazine and hexamethonium was reduced in the combined treatments as compared with their use alone. When reserpine was used concurrently with hexamethonium the dosage requirement of the latter was reduced significantly and the blood pressure response was more stable in comparison with that following the use of hexamethonium alone. Observations on renal hæmodynamics indicate that glomerular filtration and renal blood flow were not increased with any one of the three therapeutic programmes, which indicates that the clinical improvement on these patients was probably a direct result of blood pressure reduction. S. L. W.

Sorbitol, The Diuretic Effect of. A. Leimdorfer. (*Arch. int. Pharmacodyn.*, 1954, **100**, 161.) Sorbitol injected intravenously into hydrated anæsthetised dogs induced a diuresis lasting about an hour. Urinary output of sodium and chloride were raised and potassium output unchanged. Combined administration of mersalyl-theophylline or thiomerin with the sorbitol produced a much greater diuresis than did sorbitol alone, even where the dose of the mercurial given alone, under the same conditions, had little or no effect. During sorbitol administration there was a likelihood of accumulation of NPN in the blood and depletion of chloride. It was suggested that sorbitol might be of value in oliguric conditions. G. P.

Sulphones and Sulphoxides, the Therapeutic Activity of, in Experimental Tuberculosis of Guinea-pigs. S. K. Gupta and R. N. Chakravarti. (*Brit. J. Pharmacol.*, 1955, **10**, 113.) On the assumption that a lipophilic drug would be capable of reaching lipid-rich mycobacteria and harbouring tissues, a series of unsymmetrical sulphides, sulphoxides and sulphones, carrying an alkylamino group at one end and a free or potentially free amino group at the other, have been synthesized. The drugs were investigated for antituberculous activity in guinea-pigs infected with the H37Rv strain of *Myco. tuberculosis*, comparing the activity with dihydrostreptomycin, isoniazid and *pp'*-diaminodiphenylsulphone. Two of the series, SN 44 (*p*-ethylamino-*p'*-aminodiphenylsulphone) and SN 47 (*p-iso*butylamino-*p'*-aminodiphenylsulphone), had activity comparable with dihydrostreptomycin sulphate and isoniazid. None of the drugs produced any toxic symptoms in the animals and the appearance of the tissues of the lung, liver, spleen and kidney showed no damage attributable to the drugs.

G. P.

Surface-active Polyoxyethylene Ethers, Antituberculous Effects of. J. W. Cornforth, P. D'A. Hart, G. A. Nicholls, R. J. W. Rees and J. A. Stock. (*Brit. J. Pharmacol.*, 1955, **10**, 73.) The preparation and separation of linear condensation products of *p*-octylphenol with formaldehyde, including homogeneous dicyclic and tricyclic compounds, are described, together with the preparation of macrocyclic condensation products of formaldehyde with *p-tert.*-butylphenol and *p-tert.*-octylphenol. Condensation of each product was then effected with ethylene oxide. The final compounds were investigated for *in vitro* tuberculostatic activity against the H37Rv strain of *Myco. tuberculosis* and for *in vivo* activity in mice infected with the same strain. Some members of the series showed high *in vivo* activity comparable with that of streptomycin. None of those compounds having *in vivo* activity had any tuberculostatic activity *in vitro*, even in high concentration, nor was any tuberculostatic substance detected in the blood or tissue fluids from treated animals. It was suggested

that the action of these compounds *in vivo* was indirect, through the host, rather than by a direct antibacterial action. The ethylene oxide chain length was critical in determining the *in vivo* activity; peak activity was found with compounds having chain lengths of 15 to 20 units. The type of activity also changed with increasing chain length from antituberculous —→ inactive —→ "pro-tuberculous" (where the average length was 45 units or more, the infection was enhanced by the agent). This change was accompanied by a decrease in the lipophilic/hydrophilic ratio. The site of activity may be the monocytes, which have been shown to be altered in some way by one of these agents (Mackaness, *Amer. Rev. Tuberc.*, 1954, **69**, 690). This is further supported by the observation that the compounds enter the monocyte *in vivo*. It seems likely that the chemotherapeutic activity of the compounds is related in some way to their surface-active properties. G. P.

Teridax, Absorption and Excretion of. P. L. Perlman, R. E. Kosinski and D. Sutter. (*J. Amer. pharm. Ass., Sci. Ed.*, 1955, **44**, 69.) When a single oral dose of 3 g. of a new cholecystographic agent, teridax (2:4:6-triiodo-3-hydroxyphenylpropionic acid) was administered to fasting male adults, iodine equivalent to 17–23 per cent. of the dose was recovered from the urine in the following 48 hours. Blood iodine levels reached a maximum after 6 to 8 hours and then decreased rapidly although traces of iodine could be detected up to 98 days. When iopanoic acid was administered in a similar dose, 22–29 per cent. was eliminated in the stools and very small amounts in the urine. Blood iodine levels reached a maximum after about 10 hours and then declined slowly. Both teridax and iopanoic acid were better retained when given to fasting patients. In dogs and rats, teridax was mainly excreted in the urine, only traces being found in the stools. Tissue analyses in dogs indicated that the remaining iodine was stored in the liver, skin, fat and muscle.

G. B.

Thiobenzilic Acid Esters and Related Compounds, Spasmolytic Properties of. M. W. Parkes. (*Brit. J. Pharmacol.*, 1955, **10**, 95.) A series of esters of thiobenzilic acid of the general structure $Ph_2C(OH)CO.S.(CH_2)_nNRR'$, together with some benzilic acid esters, and ethers and thioethers of the type $Ph_2C(OH)CH_2.O.(or.S.)(CH_2)_nNRR'$, were tested for spasmolytic activity on the isolated ileum of the guinea-pig, against contractions induced by acetylcholine, histamine, barium and potassium chlorides, and nicotine. Many of the compounds had a much greater spasmolytic action against barium, potassium and nicotine than had papaverine. In the majority of cases this effect was specific, and anti-acetylcholine and antihistamine activity were low. This specificity suggests a mode of action different from that of papaverine and is probably at the ganglionic level. This was borne out by the activities of the compounds on other tissues; on the isolated intestine of the rabbit and the rat they were much less active and no compound equalled papaverine in spasmolytic activity on the rat uterus, guinea-pig and rabbit tracheal muscle and on the coronary vessels of the isolated rabbit heart. A marked discrepancy was found when comparing the spasmolytic potencies of the series against barium and nicotine on the ileum of different strains of guinea-pig, although the potency of papaverine varied only slightly, as did the response of the tissue to the stimulant drugs. This may imply differences in the extent to which the nervous network of the intestine is concerned in the response to barium and nicotine. The antagonism of barium as a criterion for papaverine-like spasmolytic activity seems questionable on the above grounds. G. P.