ABSTRACTS OF PAPERS PUBLISHED IN OTHER JOURNALS

CHEMISTRY

ALKALOIDS

***Veratrum album*, Alkaloids of.** H. R. Hegi and H. Flück. (*Pharm. Acta Helvet.*, 1956, **31**, 428.) The alkaloids of the leaves of *Veratrum album* L. have received little attention. The authors have extracted the alkaloids from the leaves, and separated and identified them chromatographically, full details being given of the chromatographic methods used. The alkaloidal mixture from the leaves differed considerably from that of the root. The latter contained protoveratrin (A and B), rubijervin, jervin and veratrobasin, which could not be detected in the leaves of the same plants, although in some other samples of leaves traces of some of these alkaloids were observed. In all the samples of leaves which were examined there was a dominant alkaloid which could amount to one half of the total alkaloids and which was never found in extracts of subterranean organs. Provisionally this was called alkaloid X. In addition there were found on the paper chromatographs from the leaf extracts, in all, 6 to 13 indications of alkaloids which could not be identified with any of the pure alkaloids available. It is to be assumed that at least some of these would be identical with already known alkaloids from the subterranean parts of the plant. G. M.

ANALYTICAL

Apomorphine Hydrochloide, Titration of, in Non-aqueous Media. A. Paulsen. (*Medd. Norsk Farm. Sels.*, 1956, **18**, 145.) With mercuric acetate, apomorphine hydrochloride gives a blue colour, due to reaction of a phenol group; it is therefore not possible to titrate the hydrochloride directly with perchloric acid in the usual way. It was found, however, that on titration with perchloric acid the blue colour changes to red at the end point. If on the other hand the solution of apomorphine hydrochloride in glacial acetic acid is cooled to below 15° before the addition of mercuric acetate, it remains colourless and the titration may be carried out with perchloric acid in the usual way using crystal violet as indicator. Two methods of titration are therefore recommended. In the first, 0·03 g. of apomorphine hydrochloride is dissolved in 30 ml. of glacial acetic acid, the solution is cooled to 30° and 10 ml. of 5 per cent mercuric acetate is added. The solution is then titrated with 0·1N perchloric acid in glacial acetic acid until the colour changes from blue to a bright red. In the second method the solution in glacial acetic acid, as above, is cooled to 10 to 15° before the addition of dioxan and mercuric acetate, and the titration is done with crystal violet as indicator. G. M.

Barbiturates, Toxicological Detection of. J. W. Huisman. (*Pharm. Weekbl.*, 1956, **91**, 505.) In cases of barbiturate poisoning it is important to detect with certainty the presence of the compound in the gastric contents or rinsings. A simple method is to dilute 1 part of the rinsings with 9 parts of water, and filter: 5 ml. of the filtrate is treated with 5 ml. of N sodium hydroxide and the absorption is measured between 225 and 260 mμ against a blank composed of

5 ml. of the filtrate diluted with 5 ml. of water. If no distinct maximum and minimum are obtained then a lesser dilution should be examined. Under these conditions barbiturates show a maximum at 250 to 255 mμ, and a minimum at 230 to 235 mμ. *N*-Substituted barbiturates show an absorption curve different from the other barbiturates, although in fact they are rapidly decomposed in the alkaline solution. The method may also be applied to urine, diluting with 99 parts of water, but in all cases the minimum is displaced towards greater wavelengths and may be found at 240 to 245 mμ. In such cases a preliminary extraction with chloroform is recommended. G. M.

Cocaine, Procaine and Amethocaine, Spectrophotometric Determination of. M. J. Pro, R. A. Nelson, W. P. Butler and A. P. Mathers. (*J. Ass. off. agric. Chem.*, 1956, **39**, 957.) In order to detect procaine and amethocaine as diluents in samples of cocaine, and to perform a simultaneous assay of these in a mixture using small samples, e.g., in solutions containing about 10 to 20 parts per million of each substance, it was found that wider separation of ultra-violet absorption peaks was obtained if the sample was hydrolysed in alkaline solution to give the sodium salts of respective aromatic acids, viz., benzoic, *p*-amino-benzoic and *p*-butylaminobenzoic acids resulting from the hydrolysis of cocaine, procaine and amethocaine respectively. Experimental details are given together with equations for calculating the concentrations of each substance from the intensity of absorption at the three respective peaks involved. Moreover, infra-red spectra are shown to be of use in qualitative identification of the pure and mixed compounds. D. B. C.

Gelatin, Detection of Micro Quantities of. P. Davis. (*J. appl. Chem.*, 1956, **6**, 413.) This method was devised for the detection of very small amounts of gelatin inside the silver halide grains of photographic emulsions. It depends upon the ability of gelatin to prevent the colour change from red to blue of a gold sol under standard conditions and is adapted for use in the presence of large concentrations of electrolyte, e.g., 0·4M sodium thiosulphate containing silver halide. Some twenty to thirty-fold concentration of the gelatin is achieved by a foaming procedure, details of which are given; 80 to 90 per cent recovery could be achieved. The ability of the concentrate to retard change of colour of the gold sol is then compared under standard conditions, against a blank containing no gelatin, with the effect produced by known amounts of gelatin. Using the foaming technique, the method is sensitive to as little as 4×10^{-8} g./ml. of gelatin. The method can be made semi-quantitative and is probably applicable to many other substances. D. B. C.

Menthol in Peppermint Oil, Determination of, by Chromatographic Analysis. S. K. Hamarneh, M. I. Blake and C. E. Miller. (*J. Amer. pharm. Ass., Sci. Ed.*, 1956, **45**, 713.) Solutions of menthol in chloroform give a red colour when treated with *p*-dimethylaminobenzaldehyde reagent, and this is the basis of a quantitative determination. A standard curve is prepared by treating known quantities of menthol in chloroform solution with the reagent, and measuring the colour after 2 hours, using a photoelectric colorimeter with a filter transmitting in the 500 to 570 mμ region. Using 1 ml. of chloroform solution with 5 ml. of reagent, Beer's law is obeyed for quantities of 0·01 to 0·13 mg. of menthol. In the determination of menthol in peppermint oil a preliminary separation is necessary to remove menthyl acetate, which undergoes the same colour reaction as free menthol. A sample of oil is placed on a silicic acid column and washed through with chloroform. The free menthol

appears in the early fractions of the eluate and may be determined as above. Menthyl acetate appears in the later fractions and so does not interfere in the determination. G. B.

Narcotine, Papaverine, Codeine, Strychnine and Brucine, Semimicro Determination of. B. Buděšínský. (*Československ. Farm.*, 1956, **5**, 579.) The alkaloids narcotine, papaverine, codeine, strychnine and brucine form iodobismuthate complexes in acid solution with a reagent containing bismuth ethylenediaminetetra-acetate (0·028M) and potassium iodide (0·112M), an equivalent amount of ethylenediaminetetra-acetic acid being liberated; the liberated acid is determined by titration with zinc sulphate solution. The reagent is prepared by dissolving 10 g. of crystalline sodium sulphite, 19 g. of potassium iodide and 10·6 g. of disodium ethylenediaminetetra-acetate (Complexone III) in 800 ml. of water, adding 9 g. of bismuth chloride, filtering the resulting solution and making the volume of the filtrate up to one litre. 5 ml. of reagent is added to a solution containing 20 to 40 mg. of alkaloid in 0·5N hydrochloric acid. The mixture is centrifuged and a 7-ml. aliquot of the supernatant liquid is pipetted into a flask containing 30 ml. of borax buffer solution (pH 9·1). The liberated ethylenediaminetetra-acetic acid is titrated against 0·01M zinc sulphate solution with Eriochrome Black T as indicator. A blank experiment is also carried out. The method can be used to determine the alkaloids in mixtures provided that tertiary amines, quaternary ammonium salts and the corresponding sulphonium, phosphonium and arsonium compounds are absent. E. H.

Reserpine, Contribution to the Analysis of. J. Reichelt. (*Československ. Farm.*, 1956, **5**, 516.) Reserpine forms a 1 : 1 addition compound with methyl orange and this reaction can be used for the colorimetric determination of reserpine in tablets. A weighed powdered sample containing 0·5 mg. of reserpine is shaken with 10 ml. of water in a separator; 10 ml. of sodium phosphate ($Na_2HPO_4.12H_2O$) solution (25 per cent) is added and the solution is extracted with four 25-ml. quantities of chloroform, the extracts being filtered through cotton wool. The volume of the combined extracts is made up to 100 ml. A 25-ml. aliquot of this solution is shaken for 3 minutes with 5 ml. of a freshly prepared solution containing 0·1 per cent of methyl orange and 4 per cent of boric acid. The chloroform layer is separated and dried with sodium sulphate. To 5 ml. of the dry solution 1 ml. of ethanolic sulphuric acid (prepared by adding 1 ml. of concentrated H_2SO_4 to 40 ml. of ethanol and diluting the cooled solution to 50 ml. with ethanol) is added. The intensity of the colour produced is measured in a Pulfrich photometer with filter S53. The reserpine content of the tablets is determined from a calibration curve constructed from results obtained on solutions of pure reserpine. Reserpine can be detected in tablets by paper chromatography on Whatman No. 1 paper with formamide-benzene as a solvent system. The reserpine spots can be observed in ultra-violet light. E. H.

Sodium Tetraphenylboron as an Alkaloid Precipitant. O. Aklin and J. Dürst. (*Pharm. Acta Helvet.*, 1956, **31**, 457.) This reagent gives a precipitate with the majority of aliphatic amines, quaternary ammonium bases and heterocyclic bases. For use in the quantitative gravimetric determination of alkaloids, the most important factors are thorough washing of the precipitate, and drying, the latter at a temperature not exceeding 80°. Satisfactory results were obtained in the assay of papaverine by precipitation (at pH 5 and 70°) and of strychnine (at pH 5·5 and 70°). G. M.

BIOCHEMISTRY

GENERAL BIOCHEMISTRY

Narcotic Drugs, Enzymatic *N*-Demethylation of. J. Axelrod. (*J. Pharmacol.*, 1956, **117**, 322.) Enzyme systems in rat liver homogenates which *N*-demethylate morphine and its congeners, methadone and pethidine were studied. Tissue homogenates from kidney, brain, muscle and spleen of the rat were also examined, but these had no demethylating activity. In the liver the enzymes are located in the liver microsomes and require reduced triphosphopyridine nucleotide, oxygen and other cofactors for activity. Rat whole liver homogenates had relatively little activity, but when these were differentially centrifuged and the nuclei and mitochondria removed, considerable demethylating activity was observed in the remaining fractions. The inhibitory factor present in nuclei and mitochondria was heat-labile. Rabbit whole liver homogenates, in contrast to those of the rat, had the same demethylating activity as the isolated microsome and supernatant fractions, indicating the absence of inhibitory factors in the nuclei and mitochondria. There was also some species difference in enzyme specificity: rabbit liver demethylated (−)-methadone and pethidine about twice as effectively as rat liver, whereas rat liver was the more active on morphine. Only small amounts of enzyme activity were demonstrable in guinea pig's liver and none in mouse liver. There was also a marked sex difference: liver from male rats had ten times the activity of those from females, using morphine as substrate. After oestradiol administration to male rats, there was a marked fall in enzyme activity. Similarly, in testosterone-treated females, enzyme activity rose. G P.

BIOCHEMICAL ANALYSIS

Chlorpromazine in Biological Material, Estimation of. N. P. Salzman and B. B. Brodie. (*J. Pharmacol.*, 1956, **118**, 46.) A method is described suitable for the estimation of the plasma levels of chlorpromazine in animals receiving large doses, but not sufficiently sensitive for assay in humans receiving therapeutic doses. To 1 to 4 ml. of urine or plasma add 1 ml. of 10 per cent sodium hydroxide and 25 ml. of heptane containing 1·5 per cent of *iso*amyl alcohol. Shake for 30 minutes and transfer 20 ml. of the heptane phase to a stoppered bottle containing 8 ml. of 0·1M acetate buffer, pH 5·6. Shake 5 minutes and seperate the two phases by centrifuging. Transfer a 15 ml. aliquot of the organic phase to another glass stoppered bottle containing 5 ml. of 0·1M hydrochloric acid, shake for 5 minutes, separate by centrifuging and remove the organic phase. Transfer about 3 ml. of the aqueous phase to a quartz cuvette and determine the optical density at 255 and 270 mμ. The biological "blank" is also measured at both wavelengths and the optical densities subtracted from the unknown sample. Standards are prepared by dissolving the compound in water and preparing final dilutions in 0·1N hydrochloric acid. The amount of chlorpromazine, in μg., in the sample is $\frac{U_a - U_b}{S_a - S_b} \times C \times 5 \times \frac{\bar{5}}{3}$ where U_a and U_b are the optical densities of the unknown at 255 and 270 mμ respectively after correction for blank. S_a and S_b are the optical densities of the standards at these wavelengths. C is the concentration of chlorpromazine in the standard in μg./ml. For tissues use homogenates in 0·1N hydrochloric acid. For the estimation of chlorpromazine sulphoxide, extract from the biological material

and seperate from chlorpromazine by shaking the heptane phase with 0·1M acetate buffer as described in the chlorpromazine method. A 5 ml. aliquot of the buffer is acidified with 1 ml. of 1N hydrochloric acid and the optical density of the solution determined at 275 mμ. A study of the metabolism of chlorpromazine in the dog showed it to be metabolised almost completely, but slowly because of its extensive localisation in various tissues. A major metabolite of chlorpromazine was found to be the sulphoxide and this was shown to have a sedative action on dog and man. G. F. S.

PHARMACOGNOSY

***Atropa belladonna*, Formation of Alkaloids in.** D. Daleff, N. Stojanoff, B. Awramowa, G. Deltscheff and I. Drenowska. (*Pharm. Zentralh.*, 1956, **95**, 437.) The development of alkaloids in *Atropa belladonna* was investigated at five stages of growth. The highest content (over 1 per cent) was found in the roots during the period of bud formation; in the aerial parts the maximum was found during bud formation and at the commencement of flowering. A considerable alkaloidal content was found in the thin roots, the root stumps, the upper stem parts and ripe fruits. These have not in the past been used as galenicals, but it is suggested that they should be considered. The content of wild plants from different regions showed considerable differences, and in one case an alkaloidal content of 1·27 per cent in the roots and 0·74 per cent in the leaves was observed. This appears to indicate that the selection of plant material to give a high concentration of alkaloids would be worth while. G. M.

***Atropa belladonna*, Lyophilised, Extraction of Constituents of.** E. B. Sommers and E. P. Guth. (*J. Amer. pharm. Ass., Sci. Ed.*, 1957, **46**, 55.) Leaves were collected and dried in an oven at 50° for 36 hours, and other samples were packed in solid carbon dioxide immediately after collection, and subsequently freeze-dried. All the dried samples were comminuted to No. 20, 40 or 60 powder, and examined for moisture content, total extractive, total alkaloids, chlorophyll and sugar. The total alkaloidal content and rate of extraction were similar for oven- and freeze-dried samples, but freeze-dried samples contained more chlorophyll, particularly chlorophyll A. Oven-dried samples yielded more extractive to a mixture of 3 volumes of ethanol and 1 volume of water, partly accounted for by increased nitrogenous extractive and carbohydrate content. G. B.

Digitalis, Potency of, at Different Stages of Growth. D. H. E. Tattje. (*Pharm. Weekbl.*, 1956, **91**, 541.) The assay method of Tattje and van Os was extended by a determination of the gitoxigenin content by the Tattje reagent, the aglycones being obtained by boiling with N hydrochloric acid in 25 per cent ethanol followed by extraction with chloroform. The total aglycones were then determined by the Baljet reaction, and the gitoxigenin by the Tattje reaction. The molar extinctions of digitoxin and gitoxin (Baljet reaction), after boiling with acid, are 17,600 and 15,600 respectively: that of digitoxigenin is increased by treatment with acid to from 17,200 to 18,200: that of gitoxigenin from 13,500 to 14,800. These values are used for the assay of the drug. Assays of young and full grown leaves of one year digitalis plants, collected at different seasons, showed that the total aglycone content of full grown leaves showed a

maximum at the beginning of July (4½ to 5 months after sowing). Following a drop, a second somewhat lower maximum occurs in October. With young leaves the total aglycone content is highest at the end of August, that is a month later than with full grown leaves. A striking feature is the marked rise in the ratio gitoxigenin: total aglycones, from 17 to 35 per cent. The content of crude fibre, calculated on the dry material, ranged from 6·8 to 13·8 per cent, being highest in August. The true ash content (sand-free) varied from 6·6 to 10·7 per cent: the Dutch official limit of 10 per cent is thus too strict. G. M.

Vitamin K and Naphthaleneacetic acid, Effect of, on *Datura stramonium*. B. Lowén. (*Svensk farm. Tidskrift*, 1956, **32**, 737.) Young plants of *Datura stramonium inermis* "Caspers" were sprayed with a water-soluble vitamin K analogue, stated to be 2-methyl-1 : 4-naphthaquinone sodium disulphate or with "naphthaleneacetic acid", or a mixture of the two. Some plants were sprayed once only with vitamin K analogue, 50, 150 or 300 p.p.m., while others were sprayed twice with K analogue, 50 p.p.m., naphthaleneacetic acid 50 p.p.m. or 50 p.p.m. of each. Three weeks after each spraying, leaves were collected and assayed for alkaloids. At the first collection a single spraying of K analogue 50 p.p.m. was found to increase the fresh weight, dried weight and alkaloidal content per leaf. In plants treated with 150 and 300 p.p.m. the effect was substantially greater, and the effect persisted longer when the larger amount was applied. Of the plants sprayed twice, the greatest increase was found in those plants treated with K analogue, a smaller increase occurred in those treated with K analogue and naphthaleneacetic acid and no increase in those treated with naphthaleneacetic acid only. The same effect was obtained by spraying once with a high concentration or several times with a low concentration of K analogue. G. B.

PHARMACOLOGY AND THERAPEUTICS

Adrenaline and Noradrenaline Release from the Cat Adrenal Gland. K. R. Butterworth and M. Mann. (*Nature, Lond.*, 1956, **178**, 1234.) The adrenal glands of atropinised cats were depleted of their amine content by repeated doses of acetylcholine. In all experiments one gland of the animal was used as a control and the depleted gland compared with it. It was found that there was an equal percentage loss of adrenaline and of noradrenaline and that this was irrespective of the degree of depletion, which ranged from 7 to 86 per cent. Correlating the amines lost from the depleted gland with the amines in the plasma obtained from the adrenal venous effluent, it was found that the percentages of noradrenaline in both the control gland and the depleted gland and in the plasma were the same. The total amount of amine in the plasma was equal to or a little less than the amines lost from the depleted gland. Thus there was no resynthesis of the amines while the gland was being stimulated. Making recovery experiments following the depletion, it was found to take 6 to 7 days for the total amine content of the gland to be replaced. However, by this time the amines were not present in the same proportion as they were before depletion, there being at the end of this recovery period a considerably higher proportion of noradrenaline. These experiments show that adrenaline is synthesised at a much slower rate than noradrenaline and it is inferred that it is produced from noradrenaline and not independently. M. M.

Antacids, Comparative *In Vivo* Study of. E. W. Packman, M. E. Goldberg and J. W. E. Harrisson. (*J. Amer. pharm. Ass., Sci. Ed.*, 1956, **45**, 735.) Dogs with a Pavlov simple gastric fistula were given 1 mg. of histamine phosphate subcutaneously to stimulate gastric flow. After 5 minutes a sample of gastric juice was collected and a solution or suspension of the antacid under investigation was introduced into the stomach. Gastric samples were taken every 15 minutes up to 75 minutes, the acidity of each sample being determined by titration with 0·1N sodium hydroxide using bromphenol blue as indicator. The reaction of each sample was determined by pH meter. Tests were carried out using dihydroxyaluminium sodium carbonate, aluminium hydroxide, sodium bicarbonate and calcium carbonate. Using a test dose of 5 g., all these antacids reduced the titratable acidity to a low level, and raised the pH above the desired range of 3 to 5·5. Using doses of 0·5 and 1 g., only dihydroxyaluminium sodium carbonate maintained the reaction within the limits pH 3 to 5 over the whole period of the test. Results are compared with those of the U.S. Pharmacopeia *in vitro* method. G. B.

Antacids, Comparative *In Vivo* Study of. J. W. E. Harrisson, E. W. Packman, B. Trabin and M. E. Goldberg. (*J. Amer. pharm. Ass., Sci. Ed.*, 1956, **45**, 738.) Guinea pigs were given 50 mg. of histamine phosphate in an oil/beeswax depot preparation intramuscularly each day. Daily doses of a suspension of the antacid under test were given by oral intubation. After 10 days, the animals were killed and the stomach and duodenum examined for ulceration, the degree of mucosal damage being assessed on an arbitrary scale. Dihydroxyaluminium sodium carbonate, aluminium hydroxide and calcium carbonate were found to provide partial protection against histamine-induced mucosal damage, due largely to the increased secretion of acid gastric juice. Compression of the antacids into tablets did not appear to lower their antacid action. Of the 3 commercial tablets examined the most effective was dihydroxyaluminium sodium carbonate, aluminium hydroxide was less effective, and a mixture of calcium carbonate with magnesium carbonate and magnesium trisilicate least effective. The advantages of *in vivo* tests for antacids are discussed. G. B.

Carbetapentane (Toclase); Value in Suppressing Cough Reflex. C. H. Carter and M. C. Maley. (*Amer. J. med. Sci.*, 1957, **233**, 77.) This study was undertaken to test the clinical effectiveness of carbetapentane citrate (Toclase) in relieving the cough of respiratory disorders. 557 patients were treated with carbetapentane and 134 patients were given placebo tablets. The medicament was administered either as tablets, syrup (carbetapentane 7·25 mg./5 ml.), or expectorant compounds (7·25 mg. carbetapentane and 16·67 mg. terpin hydrate/5 ml.). The amount of carbetapentane given ranged from 7 to 25 mg. per dose, and up to 150 mg. per day. Therapy usually lasted about 5 days or until the patient was free of cough. Carbetapentane was effective in reducing or eliminating the cough reflex in 91 per cent of the 557 patients, whereas the placebo was effective in only 5 per cent of the 134 cases. All dosage forms were well accepted by the patients, but the syrup and the expectorant compound were both shown to be more effective than the tablets. No side-effects occurred sufficient to warrant discontinuance of the drug. Minor undesirable effects occurred in 25 patients. These included dryness of the mouth or throat, a feeling of tightness in the chest, and a slight degree of respiratory depression. No evidence of habituation or dependence was encountered. The optimal dose was suggested to be about 7 to 10 mg. in children and 25 mg. in adults. S. L. W.

9-[(2-Chlorethyl) ethylaminomethyl] Anthracene Hydrochloride, Pharmacology of. H. Minatoya and F. P. Luduena. (*Arch. int. pharmacodyn.*, 1956, **108**, 102.) This new orally effective adrenolytic drug was studied in comparison with phenoxybenzamine hydrochloride (dibenzyline) for its adrenolytic and sympatholytic activity in anaesthetised dogs and cats, its protective action against (—)-adrenaline toxicity in mice and its effect on the blood pressure of renal hypertensive rats. It was found that the anthracene derivative in doses of 0·25 to 1 mg./kg. given intravenously, reversed the pressor effect of adrenaline and that larger doses blocked the effect of noradrenaline. It was about 5 times more active than dibenzyline in this respect. Following oral administration of the substance, it was found to have a fairly rapid onset of adrenolytic action and a long duration of effect—about 52 hours. It was effective in depressing the carotid occlusion pressor effect and the pressor effect resulting from vagal stimulation. The contraction of the nictitating membrane in response to stimulation of the cervical sympathetic was completely abolished by 0·5 mg./kg. of the drug. It reduced the toxicity of adrenaline in mice, being a little more potent than dibenzyline. In renal hypertensive rats, a dose of 0·125 mg./kg. given orally reduced the blood pressure by as much as did 2 mg./kg. of dibenzyline. The duration of hypotension was prolonged. It was found to be one-half as toxic as dibenzyline when given intravenously and two-thirds as toxic orally. In a three week sub-acute toxicity test in rats, it was well tolerated in oral doses of up to 100 mg./kg., administered 18 times. The growth rate was depressed but there were no significant haematological or pathological changes. It would therefore be of interest to study this drug clinically in the treatment of peripheral vascular diseases. M. M.

Colchamine, Pharmacology of. I. M. Sharapov. (*Farmakologiya i Toksikologiya*, 1956, **19**, No. 2, 33.) Results of a pharmacological study of colchamine are reported. This alkaloid, which is *N*-methyldesacetylcolchicine, was isolated in 1950 from *Colchicum speciosum* and is a white or yellowish crystalline powder with m.p. 181° to 182° and $[\alpha]_D^{18} = 136{\cdot}1°$ (ethanol). It is very soluble in chloroform, ethanol and methanol, insoluble in ether and soluble to the extent of 20 per cent in water. Tests on white mice, rats and rabbits showed that the general physiological action of colchamine is similar to that of colchicine. In toxic doses it produces general and respiratory depression, insensitivity to pain, loss of appetite and diarrhoea; the toxic effects are cumulative. Colchamine is, however, much less toxic than colchicine. The subcutaneous LD100 for white mice is 75 mg./kg. while that of colchicine is 5 mg./kg.; the corresponding doses for rabbits are 20 to 25 mg./kg. and 3 to 5 mg./kg. Single doses of 5, 10, or 20 mg./kg., or repeated doses of 1, 3 or 5 mg./kg. given daily for 10 days, produced anaemia and leucopenia in rats. E. H.

Dextromethorphan Hydrobromide and other Antitussives, Comparison of. L. J. Cass and W. S. Frederik. (*J. Lab. clin. Med.*, 1956, **48**, 879.) A controlled study was carried out on 63 patients with chronic cough to compare the antitussive effectiveness of dextromethorphan hydrobromide (Romilar) at two dose levels (10 mg. and 20 mg.), codeine sulphate (15 mg.), caramiphen ethanedisulphonate (Toryn) (10 mg.), and a placebo. The five materials were supplied as tablets of identical appearance, and the tablets were given 4 times a day for 10 days each, each period of drug administration being followed by 3 days of placebo medication. The cough-suppressing activity of the drugs and the placebo was recorded 3 times daily by means of a numerical scale based on 4 degrees of severity of coughing. All the drugs were shown to have antitussive

properties and to be significantly more effective for this purpose than the placebo. Ten mg. of caramiphen ethanedisulphonate was less effective than 10 or 20 mg. of dextromethorphan hydrobromide or 15 mg. of codeine sulphate. For all practical purposes it was shown that dextromethorphan hydrobromide and codeine sulphate are of equal effectiveness as antitussives on a weight basis.

S. L. W.

Dipipanone Hydrochloride in Severe Pain. R. O. Gillhespy, E. Cope and P. O. Jones. (*Brit. med. J.*, 1956, **2**, 1094.) Dipipanone, or DL-6-piperidino-4:4-diphenyl-heptan-3-one, is closely related chemically to methadone. In experimental animals the pain threshold is raised by an effective dose of dipipanone to an extent comparable with that obtained with morphine. The respiratory depressant action is stated to be less than that of an equivalent analgesic dose of morphine. The acute toxicity is about the same as that of methadone. Signs of overdosage with dogs closely resemble those occurring with morphine (constriction of the pupil, salivation, defaecation and vomiting). The mechanism of action on the bowel is probably the same as that of other morphine-like analgesics. While its main toxic action is on respiration, intravenous doses of 5 mg./kg. reduces the tone of cardiac muscle. It has some atropine-like properties. Nalorphine antagonizes the analgesic and respiratory actions of dipipanone; the effective dose is approximately the same as that required to antagonize an equi-analgesic dose of morphine. The results of administration of dipipanone hydrochloride to 100 cases of pain due to a variety of acute and chronic medical conditions, and to 100 cases of post-operative pain after major gynaecological surgery are given. Only 3 of the 200 cases failed to obtain any relief from the drug. The optimal dose was found to be 20 mg. subcutaneously in the medical cases and 25 mg. in the post-operative cases. The onset of analgesia occurred within 10 minutes and maximal relief was obtained in about 20 minutes in most cases. The effect lasted for 5 or 6 hours. There was no obvious depression of respiration or tendency to drowsiness, nor was there any local reaction or pain at the site of injection. Side-effects occurred in 4 to 5 per cent of patients, and consisted of nausea, vomiting, sweating, and giddiness.

S. L. W.

Histamine, Inhibition of Release by Sodium Salicylate and Other Compounds. C. G. Haining. (*Brit. J. Pharmacol.*, 1956, **11**, 357.) In rabbits sensitised with a modified Freund type antigen, anaphylactic histamine release in the blood was reduced by a lowering of plasma pH and by suitable concentrations of sodium chloride, potassium chloride, sodium benzoate, sodium salicylate and 3-hydroxy-2-phenylcinchoninic acid. The latter was the most effective compound being approximately eight times as active as sodium salicylate and sodium benzoate. Sodium salicylate, heparin and dextran sulphate of low molecular weight inhibited in normal blood the histamine released due to incubation with washed antigen-antibody precipitate. Sodium salicylate was effective against release due to plasma activated by antigen-antibody precipitate. Both sodium salicylate and 3-hydroxy-2-phenyl cinchoninic acid did not prevent the formation of anaphylatoxin, but inhibited its action on isolated guinea pig ileum, which was not due to histamine antagonism. Both drugs appeared to exert their inhibiting action by an extracellular mechanism and it may be that anaphylatoxin is not able to initiate the release mechanism because some factor in serum is inactivated or prevented from reaching the cell site. The possibility of a transient intracellular action cannot be ruled out. G. F. S.

Methyprylone, Central Depressant Effects of. W. Schallek, A. Kuehn and D. K. Seppelin. (*J. Pharmacol.*, 1956, **118**, 139.) Methyprylone (3:3-diethyl-5-methyl-2:4-piperidinedione, Noludar), is a new non-barbiturate sedative hypnotic. Its effects have been compared with chlorpromazine, meprobamate, and pentobarbitone. A subcutaneous dose of 45 mg./kg. was the ED50 for reducing locomotor activity in rats compared with 1·9 for chlorpromazine, 240 for meprobamate and 35 for pentobarbitone. Against induced electroshock convulsions in mice the ED50 by mouth was 150 mg./kg. compared with 150 for chlorpromazine, 200 for meprobamate, 75 for pentobarbitone and 20 for phenobarbitone. In protecting mice against leptazol convulsions the ED50 by mouth was 45 mg./kg. compared with >400 for chlorpromazine, 133 for meprobamate, 42 for pentobarbitone and 33 for phenobarbitone. The LD50 by mouth was 890 mg./kg. compared with 530 for chlorpromazine, 2000 for meprobamate, 170 for pentobarbitone and 240 for phenobarbitone. It protected dogs against vomiting induced by apomorphine in doses which caused ataxia (48 mg./kg. s.c.). Here chlorpromazine was most active, the ED50 being 0·1 mg./kg. which did not cause ataxia, meprobamate was inactive. In trained dogs it produced, like meprobamate and pentobarbitone, sleep and depression of the response to a sharp handclap. Chlorpromazine produced sedation without sleep. On the basis of doses causing equivalent duration of sleep, methyprylone was a quarter and meprobamate was one eighth as active as pentobarbitone in the dog. All the drugs produced large, slow waves in the EEG of dogs, which were greatest for pentobarbitone followed by methyprylone, meprobamate and chlorpromazine. G. F. S.

Methylphenidate Hydrochloride Parenteral Solution. J. T. Ferguson, F. V. Z. Linn, J. A. Sheets and M. M. Nickels. (*J. Amer. med. Ass.*, 1956, **162**, 1303.) Methylphenidate hydrochloride (Ritalin) was administered by intravenous injection of a 1 per cent solution in 10 mg. doses to 164 hospitalised mental patients who manifested sleepiness, lethargy, tremors, drooling, nasal congestion and Parkinson-like gait following overdosage with reserpine, promazine or chlorpromazine hydrochloride. One hundred and six of the patients showed improvement of their mental alertness and a decrease in their side-reactions within 5 to 90 minutes after the first injection, 38 responded after a second injection of 10 mg., 16 required 30 mg. before a clinical change was recorded and 4 showed no change even after 90 mg. After administering 10 to 30 mg. intravenously 3 times daily for periods ranging from 24 to 72 hours it was possible to maintain the improved condition of 151 of the 160 patients with a comparable dose of methylphenidate given orally 3 times daily. No gross change in blood pressure, pulse or respiration was recorded following the injections in 160 of the patients; 8 became apprehensive and fearful and 8 overactive. Subsequently a group of 11 chronic, regressed, underactive patients were treated with intravenous injections of the drug. Three injections of 10 mg. sufficed in every case to cause marked clinical improvement, with increased activity, sudden awareness of surroundings, and other marked changes of behaviour. These changes were obtained repeatedly, appeared promptly, were of limited duration, and were not seen after injections of a placebo. Two patients showed dramatic improvement in behaviour after 21 and 17 years respectively of extreme inactivity. Six out of 7 patients in whom the drug was continued orally after initial injections continued to show a slow, steady improvement; in the seventh patient the improvement could only be maintained by parenteral injections. S. L. W.

Morphine-Nalorphine Mixtures, Effect of, on Psychomotor Performance. R. O. Bauer and R. G. Pearson. (*J. Pharmacol.*, 1956, **117**, 258.) The effects of combining nalorphine and morphine on perceptual-motor performance were examined in 96 normal male subjects. The test used was one of compensation for random movements of four dials, by manipulation of foot and hand controls. Drug combinations used were: normal saline (placebo); morphine control, 8 mg.; morphine-nalorphine mixtures in the following proportions 8 mg.:1 mg.; 8 mg.:2 mg.; 8 mg.:4 mg.; and nalorphine 4 mg. given alone; all were administered intravenously over a two-minute period. The performance of the group given morphine was no poorer than that of the group given saline. However, with morphine-nalorphine mixtures and nalorphine alone, performance in the test decreased, with increasing dose of nalorphine. Nalorphine appeared to have a "soporific effect" in these instances. The incidence of toxic side effects of morphine was greater when nalorphine was also present. The 4 mg. dose of nalorphine given alone also caused a high incidence of side actions. G. P.

Ointments, A New Simplified Method for the Determination of Percutaneous Absorption of. H. Nogami, J. Hasegawa and M. Hanano. (*Pharm. Bull. Japan*, 1956, **4**, 347.) A method is described for studying the absorption of medicaments from ointment bases in human volunteers. The medicaments were salicylic acid and sodium salicylate in soft paraffin, a hydrophilic base, simple ointment and an absorption ointment. A weighed amount of the ointment was applied on a film 4 cm. square to the skin in the femoral region. The amount of percutaneous absorption was determined over eight or sixteen hours by (*a*) by measuring the decrease of salicylate in the ointment, or (*b*) by measuring the urinary excretion of salicylate. The results showed that salicylic acid was absorbed very well through the skin, but sodium salicylate was absorbed only slightly. The influence of the ointment base was not great, but with salicylic acid, absorption from hydrophilic ointment was less than from the other ointment bases. G. F. S.

Phenolphthalein, Carbon-14 labelled, Studies on the Fate of. W. J. Visek, W. C. Liu and L. J. Roth. (*J. Pharmacol.*, 1956, **117**, 347.) Carbon-14 labelled phenolphthalein was administered orally or intravenously to mice and dogs. Mice excreted 96 per cent of the administered radioactivity in the faeces and urine within 48 hours. No $^{14}CO_2$ was found in the expired air of the mice indicating that the phenolphthalein was not being broken down. In the dog with oral administration about 51 per cent of the radioactivity administered was present in the faeces and about 36 per cent in the urine; when the drug was injected intravenously the figures were slightly higher. When excretion in the bile was measured, after oral doses the excretion values were: faeces, 30·8; urine, 37·5; and bile 22·2 per cent. Corresponding values for intravenous administration were 11·2, 35·2 and 43·2 per cent. The drug was not concentrated in any of the organs studied. Radioactivity was found in all segments of the gastrointestinal tract after intravenous injection, suggesting that the drug was being excreted to some extent by this route. In mice, phenolphthalein crossed the placental barrier in both directions. There was no evidence of retention in the maternal tissue or the foetus. G. P.

Poliomyelitis Vaccine, Antigenic Potency of. J. E. Salk. (*J. Amer. med. Ass.*, 1956, **162**, 1451.) Groups of children who had been given different doses of a poliomyelitis vaccine in the spring of 1955 were all reinoculated in the

spring of 1956 with the same dosage of a vaccine of average potency. Quantitative studies showed both the persistence of the antibody over the course of a year and the increase in titre in response to the third dose given at this time. It was shown that to secure an optimum response to the booster injections it was necessary to give an adequate dose in the primary antigenic stimulation. After the booster injections the antibody titres equalled or exceeded those found in a group of convalescents from recent type 1 paralytic poliomyelitis; the non-living, non-multiplying virus antigen reproduced the serologic effects of naturally acquired infection-immunity. In 4617 subjects who received 3 inoculations only 224 had antibody at a level of 1:64 for all 3 types before inoculation, but 4548 had antibody at this level for all 3 types after the third inoculation. Six batches of commercially prepared vaccine were used in a study of 214 subjects as to the advantages of a second inoculation; the rise in titre produced by the second inoculation was clearly demonstrated for each batch, a low proportion of response to the first dose being converted to a high proportion of response by the second dose. It is clear that the amount of virus antigen injected is the chief determinant of the intensity of the immune response; this is reflected either in level of antibody induced or in degree of immunologic hyperreactivity effected. It has also been shown that the amount of virus antigen required to induce a maximum immulogic effect is substantially less if multiple injections are given with adequate spacing between inoculations. The two primary doses should be spaced not less than 2 weeks apart and during periods of potentially high prevalance 2 doses should be given within this short interval; in periods of low prevalance a preferable spacing would be 4 to 6 weeks or longer. The third dose, in either case, should be given about 7 months or longer after the second dose but prior to the ensuing seasonal prevalence. The indications are that immunity to paralysis is effected not only through existing antibody in the circulating blood but through the mechanism of immulogic hyperreactivity that calls forth antibody sufficiently rapidly, after exposure, to intercept invasion of the central nervous system even though pharyngeal or intestinal infection may have occurred. It is therefore conceivable that hyperimmunisation, such as tends to occur after secondary stimulation (booster), will not only limit or prevent the establishment of infection but will also limit or reduce the reservoir of infection by reducing the number of carriers in the population. Thus, poliomyelitis vaccination may bring about a sharper reduction in the amount of paralytic poliomyelitis than could be expected merely on the basis of the number of individuals vaccinated. There is indeed evidence that this is already occurring. S. L. W.

Sulfamethoxypyridazine; a Long-acting Sulphonamide. W. P. Boger, C. S. Strickland and J. M. Gylfe. (*Antibiotic Med.*, 1956, 3, 378.) Sulfamethoxypyridazine is an antibacterial sulphonamide, 3-sulphanilamido-6-methoxypyridazine (Kynex) that is readily absorbed from the gastro-intestinal tract but is excreted from the body at a very slow rate. The drug has been studied in 67 patients and administered to an additional 35 patients in doses ranging from 1 to 4 g. Following the oral administration of single doses of 1 or 2 g. doses, therapeutically significant plasma concentractions are promptly achieved and are maintained for many hours; the drug can be measured in the plasma for as long as 168 hours following a single 2 g. dose. Sulfamethoxypyridazine is slowly excreted into the urine both as free and acetylated compound; the insolubility of the acetylated form and its appearance in quantity in the urine will call for care in the use of the drug. The diffusion of the drug into the cerebrospinal fluid occurs to a greater extent than with other commonly

(ABSTRACTS *continued on p. 496.*)

A TEXTBOOK OF FORENSIC PHARMACY. By Thomas Dewar. Fourth Edition. Pp. xvi + 288 (including Index). Edward Arnold (Publishers) Ltd., London. 1957. 24s.

The first edition of this book appeared eleven years ago with the avowed object of presenting in a single volume all the forensic pharmacy which is ordinarily taught to students preparing for the qualifying examinations of the Pharmaceutical Society. Its success may be gauged by the fact that it has now reached a fourth edition and perhaps also from the relatively high proportion of passes achieved in this subject. The present edition follows the form previously adopted and all the changes in legislation, since the third edition appeared, are included. As the Society's examination appears to be largely based on what the retail pharmacist should know, it naturally follows that the book must be of considerable value as a work of reference for the practising pharmacist. Doubt, however, might be expressed on the value of including some schedules to the National Health Service Regulations. In one instance, the detail is insufficient for use in the busy dispensing department where the Drug Tariff would necessarily be consulted, and in another, even a hospital pharmacist could not be expected to produce any information on the charges for wigs or the soling and heeling of surgical boots. The students' appreciation of the revision questions might be enhanced if some of those set by the examiners during the past twelve years were indicated with the appropriate date. More cross references in the index might profitably be inserted, e.g., the Pharmacutical Society's coat of arms appears only under the main heading of "Titles and Descriptions", and to determine the conditions under which a poison may be sent through the post it is necessary to search for the entry which is "Poisons, Sale of—by Post". This book will continue to be the industrious student's sure guide to examination success and an authoritative exposition of the law.

J. ANDERSON STEWART.

(ABSTRACTS *continued from p. 494.*)

employed sulphonamides. In this series of patients 2 complained of headache following administration of the drug, 3 had mild nausea and anorexia during the first 2 days of administration, and one patient developed drug fever and became acutely ill 7 days after administration of a single 2 g. dose. S. L. W.

APPLIED BACTERIOLOGY

Acrylic Film for Surgical Dressings, Physical and Bacteriological Investigations of. B. T. Ekenstam, B. H. F. von Fieandt, F. Henn and K. B. Olow. (*Scand. J. clin. lab. Invest.*, 1956, **8**, 278.) The preparations investigated consisted of polymerised methacrylic esters dissolved in ethyl acetate (Nobecutan). Films prepared from the ethyl acetate solution were tested for tensile strength, elasticity, fatigue on folding and permeability to water and saline. Films of the polymerised butyl ester of methacrylic acid were stronger than those of the 2-ethoxyethyl ester, but the ethoxyethyl was better than the butyl ester in the elasticity and fatigue on folding tests, and was more permeable to water vapour. Solutions of the polymers in ethyl acetate were found to be sterile and to have a weak antibacterial activity. Films prepared from these solutions were initially sterile but had no antibacterial properties. Tetramethylthiuram disulphide was found to be an active antimicrobial agent, effective under aerobic and anaerobic conditions and in the presence of protein. It is soluble in the plastic solution, and the addition of 0·25 per cent yielded films active against Gram-positive and Gram-negative bacteria and fungi. G. B.