ABSTRACTS OF PAPERS PUBLISHED IN OTHER JOURNALS

CHEMISTRY

ALKALOIDS

Canescine and Pseudoyohimbine from the Roots of *Rauwolfia canescens* L. A. Stoll and A. Hofmann. (*J. Amer. chem. Soc.*, 1955, **77**, 820.) In addition to the 4 alkaloids, α-yohimbine (rauwolscine), yohimbine, serpentine and reserpine which have been isolated from the roots of *Rauwolfia canescens* L., 2 further alkaloids have now been isolated from this source. These latter were isolated from the methanol mother liquor of reserpine by means of chromatography with aluminium oxide and fractional crystallisation. One of the alkaloids, m.pt. 265 to 278° C. (cor., in vacuum tube) with decomposition, crystallised from methanol in hexagonal plates, and was found to be identical with pseudoyohimbine which was originally found in yohimbé bark. The second alkaloid, which was not identical with any known compound, was called canescine. It crystallises from 15 parts of methanol in thick pentagonal and hexagonal plates, m.pt. 230 to 234° C. (cor.) with decomposition, $[\alpha]_D - 163 \pm 2°$ (*c.*, 0·5 in pyridine). The values obtained on analysis indicate the empirical formula $C_{32}H_{38}O_8N_2$. The hydrochloride crystallised from aqueous acetone in thin rectangular plates, m.pt. 247 to 253° C. (cor.) with decomposition. It yields an equivalent of trimethoxybenzoic acid upon alkaline hydrolysis; boiling with sodium methylate in methanol gives canescinic acid methyl ester and trimethoxybenzoic acid methyl ester. From the analytical and ultra-violet data and from biogenetic considerations, the structure, 11-desmethoxyreserpine was suggested for canescine. It possesses pharmacological properties similar to those of reserpine (see p. 493); above all, it produces a marked and prolonged fall in blood pressure. A. H. B.

ANALYTICAL

Ergot Alkaloids, Paper Chromatographic Separation of. J. Tuzson and G. Vastagh. (*Pharm. Acta Helvet.*, 1954, **29**, 357.) A rapid method, which does not require specially treated paper, is as follows. The alkaloids (about 10 to 12 μg.), in the form of the free bases, are applied to the paper from an alcoholic solution, and the solvent used is composed of toluene or benzene, light petroleum and methanol (25:25:10). The paper is dried, and the spots are observed under ultra-violet light. The R_F values are as follows (using Whatman No. 1 paper): Ergotinine, 0·89; ergotoxine, 0·70; ergotamine, 0·43; ergotaminine, 0·71; ergosine, 0·48; ergosinine, 0·74; ergometrine, 0·16; lysergic acid, 0·028. G. M.

Kjeldahl Nitrogen Determination, Potassium Permanganate in the. A. E. Beet. (*Nature, Lond.*, 1955, **175**, 513.) A method for the Kjeldahl digestion process is described for semimicro (1 to 2 mg.) and micro (0·2 to 1 mg.) quantities of nitrogen. The substance is heated with sulphuric acid for about 5 minutes and after slight cooling, potassium permanganate is added in successive small amounts with shaking until the digest becomes char-free. After boiling for one minute, cooling, and adding sufficient permanganate to produce a dirty sage-green colour, digestion for a further minute completes the conversion; the ammonia is determined by steam distillation after making alkaline. About

90 per cent. of the nitrogen of coals has been converted at the char-free stage, the remaining 10 per cent. being converted by the final permanganate addition and the short after-boiling; with resistant non-charring substances, all the conversion occurs during the last period. Loss of nitrogen (or ammonia) does not occur during the digestion unless the temperature rises above 330° C. On the semimicro scale coals, cereals, feeding stuffs, leather and various alkaloids of low nitrogen content have been satisfactorily examined, while the same success, using micro-amounts, has been achieved with pyridine carboxylic acids, tryptophan, and all the alkaloids so far examined. R. E. S.

Penicillin Fermentations, Colorimetric Determination of *o*-Hydroxyphenylacetic Acid. S. C. Pan. (*Analyt. Chem.*, 1955, **27**, 65.) A method was developed based on the conversion of phenols into *p*-nitrosophenol which gives a yellow colour with ammonia. The reactions were performed entirely in an aqueous medium, giving a more sensitive assay; as little as 3μg. of *o*-hydroxyphenylacetic acid could be accurately determined by the procedure described. The *o*-hydroxyphenylacetic acid was separated from other ingredients of a cornsteep liquor medium by extraction with amyl acetate. With 2·5 volumes of amyl acetate per volume of aqueous solution, the extraction efficiency varied, within the range of 50 to 500 *o*-hydroxylphenylacetic acid per ml., between 84 and 89 per cent. An average value of 86 per cent. was therefore used as a correction factor and the recovery values, calculated on this assumption, ranged from 93·1 to 101·5 per cent., which was considered satisfactory.

R. E. S.

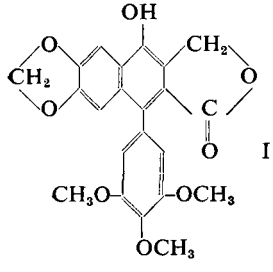
GLYCOSIDES, FERMENTS AND CARBOHYDRATES

Purpurea Glycosides A and B, Decomposition of, by Digipurpidase. K. B. Jensen. (*Acta pharm. tox., Kbh.*, 1954, **10**, 347.) Digipurpidase, an enzyme present in the leaves of *Digitalis purpurea*, hydrolyses purpurea glycosides A and B into digitoxin and gitoxin. A method is described for estimating its activity. The enzyme preparation is the dried powdered digitalis leaf after extraction of the glycosides with ethanol. The substrate is a relatively pure preparation of purpurea glycosides A and B (Sandoz). For the estimation, a volume of a methanol solution of the substrate, corresponding to 70 to 90 μg. of the glycosides, is transferred to a 2-ml. test tube using a micrometer syringe. After evaporation of the methanol, 25 mg. of the enzyme preparation is added and 1·0 ml. of a phosphate buffer solution at *p*H 5·9. The tube is shaken in a water bath (different times and temperatures were used in the investigation), 0·4 ml. of methanol is then added and the tube incubated at 20° C. in water. The enzymatic hydrolysis is followed by fluorimetric determination of the primary glycosides after paper chromatographic separation of the split products. A mixture of acetone, chloroform and formamide is used for development of the chromatograms. The results show that increasing temperature accelerates the glycoside-cleaving action of digipurpidase reaching a maximal at 60 to 65° C., but it is accompanied by an increasing inactivation of the enzyme. Previous heating of the enzyme preparation showed incomplete inactivation at 80° C. for 4 hours and little inactivation at 50 to 60° C. It is concluded that in the drying of digitalis leaves extensive cleavage of the glycosides will occur unless a temperature of 80° C. is rapidly attained throughout the leaf mass. The leaf will not be stabilised if drying is stopped as soon as the leaf is dry enough for powdering. Enzymatic activity of digipurpidase is considerably inhibited by 20 per cent. v/v of ethanol or methanol. During the extraction of digitalis leaves with 70 per cent. ethanol little hydrolysis should occur. G. F. S.

***Syrenia angustifolia*, Cardiac Glycosides of.** N. P. Maksyutina and D. G. Koleskikov. (*Aptechnoe Delo*, 1954, **3**, 18.) A preparation containing the total glycosides of *Syrenia angustifolia* was obtained by extracting the whole ground herb with ethanol, evaporating the extract to a syrup, extracting with water then with chloroform-ethanol and finally chromatographing on an alumina column. After removal of chloroform-soluble impurities, a bright yellow powder, termed "Corglisan," was obtained (4–5 g. from 10 kg. of herb). The biological activity on cats was 0·27 mg./kg. It gave positive Liebermann, Keller-Kiliani and Legal reactions. On acid hydrolysis, 15 g. of "Corglisan" yielded 7 g. of an aglycone fraction. This was dissolved in benzene and chromatographed on alumina, the column being eluted successively with benzene, benzene-chloroform, chloroform, chloroform containing increasing proportions of ethanol and finally with pure ethanol. Forty fractions were collected and 3 crystalline compounds were obtained: (i) m.pt. 185–6° C., crystallising in needles from methanol, (ii) m.pt. 198–200° C. and (iii) m.pt. 174–5° C. Paper-chromatography showed one of the compounds to be identical with strophanthidin. Two sugars were obtained from the hydrolysis liquor; one of these was soluble in acetone and gave a positive Keller-Kiliani reaction. E. H.

PLANT ANALYSIS

Dehydropodophyllotoxin, a New Compound Isolated from *Podophyllum peltatum* L. H. Kofod and C. Jorgensen. (*Acta. chem. scand.*, 1954, **8**, 1296.) During chromatography of podophyllin using sorbed formamide as a stationary phase and benzene as eluant, an intense blue fluorescence of certain fractions of the eluate between those containing podophyllotoxin and those containing α-peltatin was observed. Paper-chromatographic analysis of these eluates revealed five and possibly six different spots detectable by their blue fluorescence in ultra-violet radiation. A substance m.pt. 272 to 274° C. was isolated from the largest spot and the yield corresponded to 0·1 per cent. from podophyllin. Formula I is proposed for the substance which has been named dehydropodophyllotoxin. A. H. B.



I

***Podophyllum emodi* Wall. *var. hexandrum* (Royle), Chemical Examination of.** S. C. Caakravarti and D. P. Chakraborty. (*J. Amer. pharm. Ass., Sci. Ed.*, 1954, **43**, 614.) Powdered roots and rhizomes were extracted with light petroleum in a Soxhlet apparatus, and crystalline podophyllotoxin was obtained on cooling the extract in a freezing mixture. A viscous brown oil with a pungent odour was obtained from the mother liquor; yield 0·75 per cent. of the weight of material extracted. Resin was obtained by the method described in the B.P. 1948 for podophyllin (yield 7·3 per cent.). It contained 3·68 per cent. of the pungent oil. After purification by the removal of tar, the resin was submitted to chromatographic analysis on an activated alumina column, using a mixture of equal volumes of benzene and dehydrated ethanol as developing solvent. Podophyllotoxin (32 per cent.), picropodophyllin (0·33 per cent.) and the yellow pigment quercetin (6 per cent.) were isolated from the resin. G. B.

BIOCHEMISTRY

GENERAL BIOCHEMISTRY

Angiotonin (Hypertensin), Purification of. C. A. Kuether and M. E. Haney. (*Science*, 1955, **121**, 65.) A method is described for preparing preparations of angiotonin of a higher purity than previously reported. The highly purified preparation was unstable and lost pressor activity, rapidly deteriorating to a residual activity of about 500 AU/mg. G. F. S.

Kynurenine, Investigation on the Excretion of, in Humans. M. Špaček. (*Canada J. Biochem. Physiol.*, 1955, **33**, 14.) Kynurenine is a derivative of tryptophane which appears to be present in human urine. 24-hour specimens of urine from physically well psychotics, old people and college students, were analysed. Over a period of 4 days values for one person were fairly constant unless changes occurred in the patients condition or diet. Kynurenine excretion varied independently of the excretion of creatinine. Unusually high or low concentrations of kynurenine were independent of the *p*H of the urine. The indican reaction was often positive in urines containing large amounts of kynurenine. Elimination of tryptophane from the diet made little difference where there was no tendency to excrete kynurenine, but in cases with abnormal concentrations on a mixed diet the excretion tended to return to normal values. Comparatively large doses of tryptophane were needed to affect urinary kynurenine. Of the vitamins, pyridoxine had no consistent effect, but there was a decrease after nicotinamide. No sex differences were found, but there were increasing concentrations of kynurenine with increasing age. G. F. S.

BIOCHEMICAL ANALYSIS

Isoniazid in Blood Serum and Cerebrospinal Fluid, Estimation of. G. Hunter. (*Brit. med. J.*, 1955, **1**, 585.) The method is a modification of that of Cuthbertson *et al.* applicable to 1·25 ml. of sample. With either material protein is coagulated and removed by warming with acetic acid and centrifuging. The supernatant liquid is heated in a boiling water bath with picryl chloride solution, and the mixture is shaken with acetic acid and butanol. After centrifuging again, the butanol layer is separated and its optical density at 500 mμ is determined. A calibration curve is constructed from aqueous solutions of known strengths of isoniazid. A control determination is conducted at the same time and the value deducted from the observed value. This method makes it possible to determine isoniazid added to serum within about 70 to 95 per cent. of the amount added. H. T. B.

Morphine, Rapid Method for the Estimation of. J. M. Fujimoto, E. L. Way and C. H. Hine. (*J. Lab. clin. Med.*, 1954, **44**, 627.) A method is described for the estimation of morphine in body fluids. For total morphine (bound plus free) acidify 15 ml. of urine with 1·5 ml. of concentrated hydrochloric acid in a 50 ml. glass-stoppered centrifuge tube. Stopper and autoclave for 30 minutes at 15 lb. pressure. Cool, add 10 ml. of 16 N potassium hydroxide and 20 ml. of *n*-butanol. Shake for 15 minutes, centrifuge and transfer a 15 ml. aliquot of the butanol layer to a centrifuge tube containing 22 ml. of N sulphuric acid. Shake for 3 minutes and centrifuge. Remove the butanol layer by aspiration and transfer 20 ml. of the acid layer to another extraction tube containing a drop of phenolphthalein indicator. While

agitating the tube, add concentrated potassium hydroxide until pink. Add approximately 1 g. of sodium bicarbonate and shake until dissolved. Add 21 ml. of chloroform and shake for 5 minutes. Centrifuge and aspirate the upper aqueous layer. Shake a 20 ml. aliquot of the chloroform layer in a centrifuge tube with 7 ml. of phosphate buffer, *p*H 5·8. Centrifuge and transfer 5 ml. of the final buffer solution of morphine to a 10 ml. volumetric flask. To this aliquot add 2 ml. of silicomolybdic acid reagent and 2 ml. of concentrated ammonium hydroxide. Stopper immediately, shake and bring up to volume with distilled water. Allow 15 minutes for full colour development and determine the optical density at 675 mμ on a spectrophotometer. After correcting for reagent blank the amount of morphine is obtained from a standard curve for morphine. For free morphine omit the hydrolysis step. The final buffer extract of morphine can also be used in ultra-violet absorption studies, as a highly specific test for morphine, since therapeutic agents possessing structural features common to morphine may interfere with its determination.

G. F. S.

Poliomyelitis Virus and Antibody, a Simplified Colorimetric Test for. M. M. Lipton and A. J. Steigman. (*Proc. Soc. exp. Biol. N.Y.*, 1955, **88**, 114.) A simplified method is described for the titration of poliomyelitis viruses and their type-specific antibodies in animal and human sera. The results are indicated by colour changes in prepared test tubes containing dispersed HeLa cells, which produce acid from glucose and change the colour of phenol red to yellow. In the presence of unneutralised poliomyelitis virus the HeLa cells are destroyed and the indicator remains red. There was mostly good agreement between the colour and the activity of cytopathogenic viruses *in vitro* determined by the microscopic examination for friable cells. G. F. S.

CHEMOTHERAPY

Cephalosporin C, a New Antibiotic containing Sulphur and D-α-Aminoadipic Acid. G. G. F. Newton and E. P. Abraham. (*Nature, Lond.*, 1955, **175**, 548.) Cephalosporin C has been isolated from a species of *Cephalosporium* in the form of its sodium salt, $[\alpha]_D^{20} + 103°$; $\lambda_{max.}$ 260 mμ $\epsilon_{max.}$ 9500; equivalent weight 480 ± 15 (titration); 470 ± 15 (X-ray measurements), and is probably $C_{16}H_{20}O_8N_3SNa,2H_2O$. In the infra-red, a band shown at 5·61 μ is characteristic of the common penicillins (and of cephalosporin N), and in the former has been attributed to C=O of the fused β-lactamthiazolidine ring system. A band at 5·77 μ could be due to an ester or lactone grouping. Cephalosporin C gives a positive ninhydrin reaction and has been shown to be a monoamino-dicarboxylic acid, having two acidic groups with pK values of 3·1 and $< 2·6$ respectively, and a basic group with a pK of 9·8. It is stable in aqueous solution at *p*H 2·5 but is inactivated and degraded at pH 12. It is not inactivated by penicillinase from *B. subtilis*, strain 569, but loses activity in the presence of penicillinase from *B. cereus* (NRRL 569). Acid hydrolysis yields 1 mole of carbon dioxide and D-α-aminoadipic acid. Treatment with 1-fluoro-2:4-dinitro-benzene and subsequent hydrolysis yields 2:4-dinitrophenyl-α-aminoadipic acid, indicating that the α-amino group is unsubstituted. The pK value of this group suggests that the α-carboxyl group is also free. Acid hydrolysis yields little if any penicillamine, though isolation of valine indicates that the carbon skeleton of penicillamine is present. Cephalosporin C shows a level of activity similar to that of cephalosporin N against *E. coli*, and an activity of 8 to 10 units/mg. against *Staph. aureus* and *Salm. typhi*. J. B. S.

PHARMACY

NOTES AND FORMULÆ

Aneurine, Stability of Solutions of. E. Pongratz. (*Pharm. Acta Helvet.*, 1954, **29**, 352.) The stability of solutions of aneurine has has been determined by using for the assay the biological method of Schopfer, which is based on the specific sensitivity of *Phycomyces blakesleeanus* for this compound. No loss of strength could be detected in a plain solution of aneurine (5 per cent.), nor in one containing, in addition, calcium glucolævulinate, ascorbic acid and cysteine. G. M.

Barbituric Acids, Decomposition of Solutions of. H. Nuppenau. (*Dansk Tidsskr. farm.*, 1954, **28**, 261.) Aqueous solutions (about 10 per cent.) of various barbituric acids (as sodium derivatives) were kept at definite temperatures for varying periods. The total amount of decomposition was determined by the cobaltamine method, and in addition the carbon dioxide produced was determined, and the final *p*H of the solutions. A selection of the results is given in the table below:—

Compound	Temperature	Time	Per cent. decomposition	Final *p*H
Allobarbitone sodium ..	20° C.	105 days	2·8	10·43
	20° C.	524 days	11·3	10·04
	30° C.	105 days	6·0	10·22
	30° C.	524 days	23·5	9·21
	90° C.	2 hours	2·7	10·43
	90° C.	10 hours	10·9	9·73
	100° C.	2 hours	5·6	10·09
Barbitone sodium	20° C.	20 days	3·2	10·46
	20° C.	100 days	18·2	10·03
	30° C.	20 days	11·4	10·33
	30° C.	100 days	43·2	9·61
	90° C.	½ hour	5·2	10·79
	90° C.	2 hours	28·1	10·16
	100° C.	½ hour	11·0	10·56
Hexobarbitone sodium ..	20° C.	24 hours	4·2	10·69
	20° C.	72 hours	10·1	10·55
	30° C.	24 hours	7·3	10·50
	30° C.	72 hours	13·9	10·50
Phenobarbitone sodium ..	20° C.	10 days	3·0	9·72
	20° C.	50 days	10·7	9·31
	30° C.	10 days	7·0	9·52
	30° C.	50 days	20·7	9·07
	90° C.	10 minutes	5·4	9·58
	90° C.	60 minutes	10·4	9·34
	100° C.	10 minutes	6·5	9·54
	100° C.	60 minutes	17·0	9·35
Amylobarbitone sodium	20° C.	14 days	3·7	10·26
	20° C.	90 days	15·1	10·04
	30° C.	14 days	8·0	10·10
	90° C.	10 minutes	2·0	9·94
	90° C.	60 minutes	8·2	9·92
	100° C.	10 minutes	4·2	9·94
	100° C.	60 minutes	17·9	9·85

The decomposition follows the curve of a monomolecular process, and the velocity constants and temperature coefficients are given. G. M.

Diphemanil Methylsulphate (Prantal Methylsulphate). (*New and Nonofficial Remedies: J. Amer. med. Ass.*, 1955, **157**, 342.) Diphemanil methylsulphate is 4-diphenylmethylene-1 : 1-dimethylpiperidinium methylsulphate and occurs as a white or nearly white, bitter, crystalline substance, with a faint characteristic

odour, m.pt. 189° to 196° C., very slightly soluble in ether, and soluble, at 25° C., in about 33 parts of water, ethanol, and chloroform. It is stable to heat and light but somewhat hygroscopic. A 1 per cent. solution has *p*H 4·0 to 6·0, and yields a brown precipitate with potassium permanganate. The picrate has a melting point of 194° to 200° C., after being dried *in vacuo* for 5 hours. When dried at 105° C. for 4 hours, diphemanil methylsulphate loses not more than 0·5 per cent. of its weight; it yields not more than 0·1 per cent. of sulphated ash. It contains 97 to 103 per cent. of anhydrous diphemanil methylsulphate, when determined by precipitation as the reineckate, and 98 to 102 per cent. when determined by hydrolysis with potassium hydroxide in propylene glycol, and precipitation of the liberated sulphate with barium hydroxide. It is a quaternary parasympatholytic agent. G. R. K.

PHARMACOGNOSY

Ergot Sclerotia, Alkaloid Formation in. Y. H. Loo and R. W. Lewis. (*Science*, 1955, **121**, 367.) The time required for alkaloids to appear in the sclerotia of cultured ergot has been investigated. A plot of tetraploid Rosen rye was inoculated over two days by spraying the flowers with a sugar-spore suspension, the spores being produced in shake cultures on a medium of 40 per cent. commercial sucrose in potato broth prepared by boiling 400 g. of sliced potatoes in sufficient water to produce 1 l. of broth when decanted. Samples each consisting of about 200 heads were collected from the plot at random 8, 10, 12, 15, 17, 19 and 26 days after the last inoculation, and the heads were dried for 2 days at 60 to 80° C., after which the sclerotia were removed and weighed. The average weights of sclerotia in mg. for daily samples were 4·9, 6·2, 7·3, 10·2, 23·2, 38·0 and 55·6 mg. respectively. Pigmentation was not complete until after the 12th day, when the sclerotia were found to be heavily pigmented. The amount and nature of the alkaloids produced was then determined. Dried pulverised samples were extracted with ammoniacal ethanol, the ethanol was removed and the alkaloids at *p*H 8 in the water layer were extracted into chloroform after which they were returned to aqueous maleic acid solution. The percentage yield of alkaloids was then determined colorimetrically by a modification of the Van Urk method with the following results: 0, 0, 0·005, 0·012, 0·05, 0·14 and 0·12 per cent. respectively. A visible absorption curve (400 to 800 mμ) of the blue reaction-product formed with the samples collected from the 12th to 26th day was identical with lysergic acid. An ergonovine type of activity was demonstrated by pharmacological assays, and paper chromatography using a butanol–acetic–water system identified ergonovine as the main component in extracts exhibiting a blue fluorescence in ultra-violet light. The authors conclude from the results that the alkaloids are synthesised in the fungus during the later stages of development. J. R. F.

***Rauwolfia sellowii*, Alkaloidal Content of.** T. A. Neubern de Toledo and R. Wasicky. (*Scientia Pharm.*, 1954, **22**, 217.) The alkaloids in *Rauwolfia sellowii* were determined by the method of Hörhammer and Rao (*Arch. Pharm. Berl.*, 1954, **287**, 75.) The content of different parts of the plant was as follows: Bark of thicker roots, 8·3 per cent.; bark of thinner roots, 3·5 per cent.; bark of twigs, 1·19 per cent.; bark of stem, 2·04 per cent.; shoots without leaves, 0·72 per cent.; leaves, 2·1 per cent. The content in the wood was practically nil. Thus the alkaloidal content decreases from the root to the ends of the twigs, though present only in the peripheral parts. The leaves should prove a useful source of the alkaloids. G. M.

PHARMACOLOGY AND THERAPEUTICS

Acetazoleamide (Diamox) Diuresis. A. Ruskin. (*Arch. intern. Med.*, 1955, **95**, 24.) Acetazoleamide, or 2-acetylamino-1 : 3 : 4-thiadiazole-5-sulphonamide, is a diuretic agent. This study is concerned with the kind, degree and length of diuresis, comparison of single and multiple dosage, possible hæmodynamic mechanisms, and possible effects on enzymes other than carbonic anhydrase. In 15 patients with cardiac failure given 3 to 6 g. of acetazoleamide by mouth in divided doses over 24 hours, the urine volume generally more than doubled in 24 hours, with marked rises in sodium and potassium excretion. While the diuresis slackened the day after the drug was given electrolytes continued to be excreted in large amounts. While diuresis was a constant effect, the urinary sodium and potassium concentration actually fell slightly in 5 and 2 of the 15 cases respectively on the first, but not on the second day. The toxic effects were mild parasthesias and drowsiness, nausea and vomiting in 3 cases, and a reversible psychosis in 1 case of nephrosclerosis with uræmia. In 3 cases of congestive failure refractory to mercurials, acetazoleamide produced a satisfactory diuresis. In many of the patients diuresis and weight loss continued for many days, up to 3 weeks, without further use of diuretics. In 12 patients with congestive heart failure a comparison of the effects of 500 mg. of acetazoleamide administered by mouth in a single dose or of 4 such doses given over 24 hours showed that diuresis was only slightly more effective in the second and third 8-hour periods after multiple doses. Acetazoleamide diuresis was found by the author to be associated with carbonic anhydrase inhibition in the renal tubules, producing an alkaline urine, excessive distal tubular excretion of potassium, and decreased tubular reabsorption of sodium and other cations, bicarbonate, and, consequently, water. Lack of toxicity in the heart and kidney was evidenced by failure to inhibit the activity of succinic dehydrogenase and adenosine triphosphatase in those organs. Such hæmodynamic alterations as may occur after acetazoleamide administration do not contribute to its diuretic effect. S. L. W.

Adrenaline and Noradrenaline, Intrathecal Injections of. S. O. Liljedahl. (*Acta physiol. scand.*, 1955, **33**, 19.) The effect of adrenaline and noradrenaline on the blood glucose and blood pressure of the cat is studied. The injection is given either into the cisterna magna or the third ventricle of the brain or as a continuous intravenous infusion. Adrenaline, when given intracisternally, produces a marked increase in the blood sugar level without raising the blood pressure. Noradrenaline, given by the same route, again has no effect on the blood pressure and has less effect than adrenaline on the blood sugar level. Injections into the third ventricle produce similar results. Continuous intravenous infusion of suitable doses of either amine causes a similar rise of blood sugar as when given intracisternally, adrenaline being 5 to 10 times more potent than noradrenaline. Again there is no effect on the blood pressure. These experiments suggest that the hyperglycæmic effect of either adrenaline or of noradrenaline, when injected into the cisterna magna or the third ventricle, is brought about by absorption of small quantities from the dural space. M. M.

Anticholinesterases and Muscle Relaxants. B. G. B. Lucas and S. Miles. (*Brit. med. J.*, 1955, **1**, 579.) Gallamine and tubocurarine act by competing with acetylcholine at the motor end-plate, while succinylcholine and decamethonium iodide act in the same way as an accumulation of acetylcholine, namely by persistently polarising the motor end-plate and rendering it insensitive to acetylcholine. Succinylcholine is hydrolysed in the same way as acetylcholine

by cholinesterase but decamethonium iodide does not depend on cholinesterase for its removal. The amount of cholinesterase in the body may therefore alter the duration of action of some relaxants, so that exposure to anti-cholinesterase substances may necessitate modification of the usual dosage of the relaxants. To test the hypothesis a comparison was made of the duration of respiratory paralysis following intravenous injection of comparable dosages of tubocurarine, gallamine, decamethonium iodide and succinylcholine into rhesus monkeys before and after a standard dose of the anti-cholinesterase sarin (*iso*propylmethyl phosphonofluoridate). The sarin was given subcutaneously in doses equal to two-thirds of the LD50, which produced miosis, salivation, respiratory distress and muscular fibrillation. The relaxants were investigated in pairs, the time being taken from the injection to the re-establishment of effective natural respiration. Blood was withdrawn for plasma cholinesterase determination at the beginning and end of the period. With tubocararine and gallamine there was a significant decrease in the period of respiratory paralysis after injection of sarin; with succinylcholine there was an increase. Sarin had no appreciable effect on the duration of action of decamethonium iodide. With the increasing use of anticholinesterases as insecticides caution is needed to avoid the possibility of poisoning by muscle relaxants other than decamethonium iodide and the same would apply to war casualties exposed to sarin. H. T. B.

Antihistamines as Adrenaline Sensitisers. K. Kuriaki and T. Uchida. (*J. Pharmacol.*, 1955, **113**, 228.) The three antihistamines used are diphenhydramine, methaphenilene and *N*-dimethylaminoethyl phenothiazine hydrochloride (Anergan). The actions of these drugs on adrenaline responses, sympathetic and vagal stimulation and on the activity of amine oxidase are studied. The preparations used are the isolated heart of the toad, the blood vessels of the hind limb of the toad, the isolated intestine of the rabbit, the blood pressure and respiration of the rabbit and the nictitating membrane of the cat. Anergan, and particularly diphenhydramine, sensitise receptors to the effects of adrenaline and sympathetic stimulation but block the effects of vagal stimulation. Methaphenilene has variable effects, sometimes increasing the response to adrenaline and sometimes decreasing it. Consistent with their ability to act as adrenaline sensitisers, diphenhydramine and Anergan inhibit the activity of amine oxidase, whereas methaphenilene produces no inhibition. Thus it is assumed that the adrenaline sensitising effect of these antihistamines is related to their anti-amine oxidase activity. M. M.

Azaserine, Effect of, on the Growth of Mouse and Rat Tumours. K. Sugiura and C. C. Stock. (*Proc. Soc. exp. Biol., N.Y.*, 1955, **88**, 127.) The effects of crude culture filtrates of *Streptomyces fragilis* and partially purified and crystalline preparations of azaserine (*O*-diazoacetyl-L-serine) have been tested against 17 mouse tumours, 5 rat tumours and 3 ascite tumours of the mouse. The effects of the filtrates were generally similar to crystalline azaserine. Azaserine had a marked inhibitory effect against 1-day-old implants of Sarcoma 180, a moderate effect on Adenocarcinoma E0771, Patterson lymphosarcoma and Mecca lymphosarcoma and on Sarcoma 180 ascites tumour, Ehrlich ascites carcinoma and Krebs 2 ascites carcinoma. There was no inhibition of any of the tumours, except Sarcoma 180, when tests were made with 7-day-old growths. Daily doses of 5 mg./kg./day inhibited Walker carcino-sarcoma 256, Sarcoma R39, Jensen sarcoma and Murphy–Sturm lymphosarcoma, but only a slight inhibitory effect on Flexner–Jobling carcinoma. G. F. S.

Benzathine Penicillin, Rectal Absorption in the Rabbit. S. Carvalho and A. Santos. (*Rev. Portugesa Farm.*, 1954, **4**, 237.) Serum levels of benzathine penicillin have been studied in the rabbit after rectal administration of 150,000 U. in suppositories with a water soluble (polyethylene glycols 6000–75 per cent. and 1500–15 per cent.) and cocoa butter base. Penicillin was detectable, using the F.D.A. method, after 10 minutes; the highest concentrations appearing between 20 minutes and 3 hours after administration of the water soluble suppository and between 30 minutes and 7 hours after the cocoa butter preparation. These were 0·35 U./ml. and 0·12 U./ml., respectively. J. R. F.

1-*n*-Butylamino-3-*p*-toluidino-2-propanol (W181), the Analeptic Action of. F. M. Berger and T. E. Lynes. (*J. Pharmacol.*, 1954, **112**, 399.) 1-*n*-Butylamino-3-*p*-toluidino-2-propanol has been shown to relieve paralysis caused by mephenesin (Berger, *J. Pharmacol.*, 1953, **107**, 250). It also has high analeptic activity in mice against phenobarbitone and benzimidazole, arousal being obtained with non-convulsant doses of the analeptic. Activity is somewhat less against hexobarbitone, pentobarbitone, thiopentone and chloral hydrate, doses of the order of twice the LD50 being necessary. Convulsions caused by W181 were prevented or lessened in severity by thiopentone, chloral hydrate, mephenesin, phenobarbitone and pentobarbitone, in that order of effectiveness. Benzimidazole or hexobarbitone in the doses used had no anticonvulsant effect against single LD50 doses. G. P.

Chlorpromazine in Psychiatric Conditions. H. E. Lehmann. (*Canad. med. Ass. J.*, 1955, **72**, 91.) This is a report on the results of chlorpromazine therapy in 238 neuropsychiatric patients. In general, the most promising application seems to lie in the treatment of the manic phase of manic-depressive psychosis, in which the drug brought about a complete remission within 40 days in 48 per cent. of cases. In conditions of chronic manic excitement which have resisted other therapeutic measures it often produces favourable results, though the drug may have to be administered for 2 or 3 months in these cases. Of 98 cases of schizophrenia complete recovery was obtained within 40 days of commencement of treatment in 28 per cent. of those patients whose symptoms had been present for 1 month or less. If much improved patients are included, 39 per cent. of 54 acute schizophrenics improved in less than 2 months sufficiently to be discharged from hospital. No recoveries and only 1 case of considerable improvement occurred among the 44 subacute and chronic schizophrenic patients, but symptomatic improvement and control was obtained in a large proportion of cases. The lowering of blood pressure calls for continued medical supervision and nursing care so long as the patient is receiving large doses of the drug. 5 per cent. of patients receiving the drug for more than a week developed allergic conditions, such as urticaria or angioneurotic œdema. 3 per cent. of patients showed gastro-intestinal symptoms, and 4 to 6 per cent. developed an extrapyramidal syndrome resembling Parkinsonism when the drug was given in large doses over a long period. Several patients with a history of epileptiform seizures developed convulsions while receiving the drug. 8 patients developed jaundice during treatment but responded well to discontinuation of the drug and supportive treatment. No untoward effects on bone marrow or kidney function were observed. Chlorpromazine differs from other short-acting sedatives because of its more selective effect on mesencephalic–diencephalic structures, thus providing a new therapeutic approach to certain troublesome psychiatric conditions. In acute psychotic breakdowns associated with affective disturbances, more specifically psychomotor excitement and

emotional tension, it may shorten or prevent full development of an attack and may be preferable to electroshock therapy. S. L. W.

Chlorpromazine in the Treatment of Intractable Hiccups. C. E. Friedgood and C. B. Ripstein. (*J. Amer. med. Ass.*, 1955, **157**, 309.) 46 men and 2 women aged from 26 to 80 years of age and suffering from intractable hiccups were treated with chlorpromazine. Symptoms had persisted from days to weeks and had not responded to heavy sedation, carbon dioxide inhalations, or any other therapy including, in 5 patients, phrenic nerve crush. A dose of 50 mg. was given intravenously and was usually sufficient to stop the hiccups; when necessary a second dose was given within 2 to 4 hours. In several of the older and debilitated patients, 25 mg. was given intravenously as the initial dose and 25 mg. intramuscularly. Of the 50 patients treated, 41 were relieved almost immediately without recurrence of symptoms. 5 patients had recurrence after at least 6 hours relief. In these, further administration reduced the intensity and frequency of the hiccups but did not effect a cure. 4 patients showed no response at all because the causal factors were not treated, such as a subphrenic abcess, or failure of a colostomy stoma to open. Good results were also obtained in patients with a milder type of hiccups by oral administration although the effect was often delayed up to 24 hours. G. R. K.

Dromoran, Fate of, in the Dog. P. Shore, J. Axelrod, C. Hogben and B. B. Brodie. (*J. Pharmacol.*, 1955, **113**, 192.) This paper describes a sensitive method for the estimation of Dromoran (3-hydroxy-*N*-methylmorphinan) in biological material and, using this method, a comparison is made of the fate of the (−)-isomer, levorphan and the (+)-isomer, dextrorphan in the body. The drug is extracted from alkaline biological material with benzene and estimated by forming a methyl orange complex. It is found that the fate of both the isomers in the dog is almost identical. About 60 per cent. appears in the urine in a conjugated form. The fate of the remainder is unknown. This transformation is rapid with a biological half-life for both isomers of less than 1 hour. This is considerably faster than that for morphine. In spite of this rapid disappearance of the drug the animal remains narcotised for a considerably longer time, suggesting that the activity of the compound might be mediated through a metabolic product. After parental administration, the drug is found in high concentration in the gastric juice. Neither levorphan nor dextrorphan is demethylated to the corresponding nor-isomer. M. M.

Erythromycin, Treatment of Neonatal Staphylococcal Infection with. J. O. Forfar, A. F. Maccabe, C. L. Balf, H. A. Wright and J. C. Gould. (*Lancet*, 1955, **268**, 584.) A trial designed to test the efficiency of erythromycin in neonatal staphylococcal infections and to determine whether resistance would appear quickly under control conditions was carried out in the maternity units of 2 hospitals. In one unit 140 cases were treated with erythromycin, in the other 80 cases were treated with erythromycin plus streptomycin to determine whether combined therapy would reduce the risk of resistant strains emerging. Treatment ranged over 2 to 9 days and the combination proved no more effective than erythromycin alone. There were no failures in the treatment of deep and superficial skin sepsis, but 8 per cent. of conjunctivitis cases did not respond. It was found by phage-typing that a limited number of strains were responsible for the cases of clinical infection. No strain of *Staph. pyogenes* developed resistance to erythromycin during the trial, the antibiotic did not interfere with the normal growth of *E. coli* in the gut, and no case of fungus or staphyloccus infection of the alimentary tract was found.

A free interchange of staphylococci between staff and infants took place and cross infection was common. The increased use of streptomycin appeared to increase the proportion of streptomycin-resistant organisms among staphylococci isolated from staff nasal carriers. J. R. F.

Hydrastine, Hydrastinine and Sparteine, Toxicity of. C. F. Poe and C. C. Johnson. (*Acta pharm. tox., Kbh.*, 1954, **10**, 338.) A comparison has been made of the toxicities of these alkaloids to albino rats and the results compared with their toxic action to micro-organisms. By the intraperitoneal route the estimates of LD50 for rats 6 weeks old, were hydrastine 104 mg./kg. and sparteine 42 mg./kg. The LD50 of sparteine was about 65 per cent. greater by the subcutaneous route. Lethal doses of hydrastine caused nervous excitation with tetanic spasms. Tested against the normal fermentative action of *Escherichia* and *Ærobacter* and on their growth, the toxicities of hydrastine, hydrastinine and sparteine were very low. G. F. S.

4-Hydroxy*iso*phthalic Acid, Analgesic and Antipyretic Activities of. G. B. Chesher, H. O. J. Collier, F. A. Robinson, E. P. Taylor, S. E. Hunt, J. I. Jones and A. S. Lindsey. (*Nature, Lond.*, 1955, **175**, 206.) 4-hydroxy-*iso*phthalic acid is a byproduct of the manufacture of salicylic acid to which it has a structural similarity. Pharmacological tests show that it has analgesic properties. In young rats, by the tail pressure method, the median effective dose was 303 (limits 261–353) mg./kg. and it had 4·1 per cent. of the activity of codeine. The LD 50 to rats was 1·071 mg./kg. (limits 968–1185). It was more effective and less toxic than aspirin. Chronic toxicity in mice was low and of the same order as aspirin. Excretion tests in rats showed 40 per cent. of a 10 mg. dose by mouth was excreted unchanged in the urine and 25 per cent. in the fæces. Antipyretic tests in rabbits showed it to be as effective as aspirin in counteracting fevers caused by a preparation of pyrogen from *Proteus vulgaris*. Clinical trials of the drug are in progress. G. F. S.

Mephenesin in the Treatment of Progressive Myoclonic Epilepsy. R. E. Kelly and D. R. Laurence. (*Brit. med. J.*, 1955, **1**, 456.) The main disability in progressive myoclonic epilepsy is myoclonus, the disease progressing until the patients exist in "status myoclonicus" and die of exhaustion and inanition within 4 to 5 years of the onset. The disease soon becomes resistant to the action of anticonvulsants. It has now been found that the myoclonus can be controlled by massive dosage of mephenesin. 5 cases are reported, of whom 4 helpless patients were restored temporarily to activity by the intravenous injection of a 1 per cent. solution of mephenesin in saline. One less serious case obtained considerable benefit from oral mephenesin, and treatment by mouth appeared to produce significant improvement in all, but in 3 cases it is too early to assess results. The drug is rapidly metabolised and the clinical effect of an intravenous injection may pass off in as little as 30 minutes, while the effect of an oral dose may last for only 1 to 1½ hours. Up to 48·5 g. of mephenesin per day has been required. When given by mouth the drug should be taken on a full stomach, to diminish the side effects, namely dizziness, drowsiness and vomiting, and may be taken partly as an elixir and partly as tablets, although the latter are absorbed less readily and probably less completely than the elixir. If the patient sips the elixir, the drug may anæsthetise the throat and this may lead to inhalation of the preparation. Of two cases reported fully, one is maintaining freedom from myoclonus on 15 g. of mephenesin carbamate per day. The second is taking a total of 30 g. per day of which 8 to 10 g. is in the form of an elixir and 20 to 22 g. as tablets. H. T. B.

***N*-Methyl-α-phenylsuccinimide (Milontin), Some Effects of, on the Central Nervous System.** W. H. Funderburk and R. T. Woodcock. (*J. Pharmacol.*, 1954, **112**, 404.) The action of *N*-methyl-α-phenylsuccinimide, an anticonvulsant drug, was studied at various levels of the cerebrospinal axis in the cat, and compared with that of trimethadione. Neither drug had much effect on the patellar reflex, or on the modification of this reflex by contralateral or ipsilateral sciatic stimulation. The electroencephalogram of the curarised cat under artificial respiration showed marked wave-slowing and sleep spindles with both depressants. Arousal responses to sensory stimulation were readily obtained with doses up to 100 mg./kg. The EEG arousal response induced by stimulation of the reticular formation activating centre was reduced with doses of 100 mg./kg. There were no changes in EEG spindle activity in mesencephalic-sectioned cats (*cerveau isolé* preparation) with doses of Milontin up to 150 mg./kg. or of trimethadione up to 400 mg./kg. The only difference between the two drugs lay in their ability to suppress cortical after-discharge, Milontin being the more potent. G. P.

2-Methyl-2-*n*-propyl-1:3-propanediol Dicarbamate (Miltown), a New Interneuronal Blocking Agent. F. M. Berger. (*J. Pharmacol.*, 1954, **112**, 413.) Miltown, an analogue of mephenesin, had a more prolonged sedative and paralysing effect than mephenesin on monkeys, cats, rabbits, rats and mice. As with mephenesin the paralysing action is located in the spinal cord, Miltown readily depressing the polysynaptic flexor reflex in the cat, when the monosynaptic knee jerk was relatively unaffected. In non-paralysing doses it antagonised strychnine- and leptazol-induced convulsions and deaths in mice. The drug also prolonged hexobarbitone sleep time and prevented the tonic extensor phase of electroshock seizures. Rats receiving 2 per cent. of Miltown in their food over a period of 15 months were lighter than controls, but otherwise showed no ill effects. The drug was active orally and did not cause nausea or emesis. There were no significant effects on respiration, heart rate or other autonomic functions. Detoxication is apparently by conjugation as the glucuronide; duration of action is about 8 times longer than that of mephenesin. G. P.

Noradrenaline and Isoprenaline, Effects of, on Neuromuscular Transmission during Partial Curarisation. F. Dybing. (*Acta pharm. tox., Kbh.*, 1954, **10**, 364.) Experiments have been carried out in rabbits recording the contractions of the flexor digitorum longus muscle obtained on stimulation of the sciatic nerve and by direct stimulation of the muscle. Constant curarisation was obtained by a continuous infusion intravenously of a solution of tubocurarine. When the muscular contractions had remained constant for 20 minutes, adrenaline, noradrenaline, or isoprenaline (*iso*propylnoradrenaline) was injected intravenously. Noradrenaline, like adrenaline, had a short anticurare effect followed by a weak augmentation of the partial neuromuscular block. Isoprenaline caused only an augmentation of the neuromuscular block with no initial anticurare effect. The directly stimulated muscle showed no decrease in contraction on the injection of isoprenaline during partial curarisation. The results indicate that the neuromuscular effects of the sympathomimetic amines do not depend upon a reduction in blood flow. G. F. S.

Pentobarbitone Anæsthesia, Potentiation of, in Mice by Isoniazid and Related Compounds. A. Goldin, D. Dennis, J. M. Venditti and S. R. Humphreys. (*Science*, 1955, **121**, 364.) The authors, while investigating enzymatically

catalysed exchange reactions, observed that several of the congeners of nicotinic acid employed in antitubercular studies prolonged the anæsthetic action of pentobarbitone in mice. The 10 to 12-week-old male mice (weighing 20 to 25 g.) used, were given the barbiturate by the intraperitoneal route and the other compounds subcutaneously. The extent of the anæsthesia produced by the barbiturate when administered 15 minutes after isoniazid was found to increase with increasing doses of the latter. Prolongation of anæsthesia was achieved with as little as 50 mg./kg. of isoniazid with doses of 60 mg./kg. of pentobarbitone. The barbiturate afforded protection against the acute toxicity of isoniazid even when administered in the initial stage of convulsive seizure. The extent of potentiation and protection appear to depend on the relative doses of the pentobarbitone and isoniazid employed. 1-*iso*Nicotinyl-2-*iso*propyl hydrazine phosphate (Marsilid), *iso*nicotinic acid amide, nicotinic acid hydrazide, 3-acetyl pyridine, hydrazine hydrate and glycine, also prolonged the anæsthesia. Although both isoniazid and Marsilid when administered simultaneously with, or 4 hours prior to, pentobarbitone were found to prolong anæsthesia, they do not appear to act in a similar manner. Marsilid 250 mg./kg. caused a 40 to 50 per cent. reduction in the dose of pentobarbitone required to induce anæsthesia in 50 per cent. of the animals (ED50). With 250 mg./kg. of isoniazid reduction of the ED50 was not significant. With a sub-anæsthetic dose of the barbiturate (30 mg./kg.), 250 mg./kg. of Marsilid induced anæsthesia, while 50 to 400 mg./kg. of isoniazid did not. The barbiturate did not protect against the toxicity of 3-acetyl pyridine, while nicotinamide did so without reducing the potentiating effect of the 3-acetyl pyridine on the pentobarbitone anæsthesia. As an inhibition of diphosphopyridine nucleotidase activity by pentobarbitone has been observed, the relationship of enzymatic transformations, involving diphosphopyridine nucleotidases, to the potentiation of barbiturate anæsthesia is under investigation. J. R. F.

Recanescine, An Alkaloid from *Rauwolfia canescens*, Pharmacological Properties of. I. H. Slater, R. C. Rathbun, F. G. Henderson and N. Neuss. (*Proc. Soc. exp. Biol., N.Y.*, 1955, **88**, 293.) The authors have isolated and characterised a new sedative alkaloid from *Rauwolfia canescens* to which they have given the name recanescine. The physical and analytical data indicate that this is 11-desmethoxyreserpine and, in a footnote to the paper, attention is drawn to a report of an alkaloid canescine from the same source by Stoll and Hoffmann, which is probably identical (see p. 480). Recanescine, as an ethyl acetate solvate, is readily soluble in glacial acetic acid and when diluted suitably, was injected intravenously into mice, rats, rabbits, cats and monkeys, which were then subjected to a number of pharmacological experiments. Where possible, similar experiments were carried out with the same dose of reserpine. From the results it was concluded that the new alkaloid retains the characteristic pharmacological activity of reserpine and therefore the methoxyl group of reserpine is not essential for the sedative and hypnotic action. J. R. F.

Reserpine, Antagonism of, to Morphine Analgesia in Mice. J. A. Schneider. (*Proc. Soc. Biol., N.Y.*, 1954, **87**, 614.) Reserpine has been found to antagonise the analgesic effect of morphine in mice, while chlorpromazine prolonged it. White mice of both sexes were subjected to a beam of heat focussed on the tip of the tail of each animal according to the method of Gross (*Helv. physiol. Acta*, 1947, **5**, C31.) The intensity of the pain stimulus was set to obtain an average reaction time of 4 seconds under control conditions. No stimulus was applied for longer than 10 seconds, each animal being stimulated twice

during the tests. The results indicate that reserpine in doses up to 10 mg./kg. s.c. did not alter the pain threshold, but when given 2 hours before a dose of morphine (10 mg./kg. s.c.) the analgesic action of the latter was reduced in proportion to the dose of reserpine. A 10 mg./kg. dose of chlorpromazine produces a slight analgesic effect, and in combination with morphine (10 mg./kg.) prolonged the analgesic effect of the latter. The author suggests that the reserpine/morphine relationship may be the result of competitive action at various sites of the central nervous system, and points out that the results show that the modes of action of chlorpromazine and reserpine differ, although they both appear to have a similar clinical effect on the central nervous system.

J. R. F.

Rheumatoid Arthritis, Treatment of, by Stimulation of the Adrenal Cortex. H. F. West and G. R. Newns (*Lancet*, 1955, **268**, 578.) Mild to moderate adrenal stimulation with corticotrophin in 11 rheumatoid patients, over 1 to 2 years, has been found so far to influence favourably the course of moderately severe rheumatoid disease. Various brands of long acting corticotrophin were used in a dosage designed to give a daily urinary output of 15 to 40 mg. of 17-ketogenic steroids. The doses, given 12 hourly, varied from 7·5 to 40 units per day, the unit being 1/3 of a U.S.P. unit. To control the level of stimulation, 24-hour urine specimens were assayed every 5 to 7 days until a suitable maintenance level had been found, and then monthly. In the 6 males, the disease had lasted from 3 months to 13 years and in the 5 females from 2 to 20 years. The former were treated over 12 to 17 months, the latter over 12 to 24 months. The average results show a general improvement. The E.S.R. fell from an average of 38 mm. to 19 mm., Hb increased from 12·3 to 13·3 g./100 ml., the white cell count increased from 8600 to 10,900, and weight from 130 to 147 lb. All patients felt better in themselves, the hand grip became stronger, and there was an improvement in physical ability. In 4 patients there was a rise in blood pressure, in 2 pigmentation appeared, and 2 showed an increase in bone erosion. A leucocytosis usually accompanied severe stimulation. A comparison with 27 patients treated with cortisone acetate reveals that the stimulation method produces better results with fewer side effects. In conclusion the authors recommend an extension of the clinical trial and express the need for a more satisfactory adrenal stimulant for long-term use than the present preparations of corticotrophin. J. R. F.

Sodium Nitrate Poisoning Treated by Exchange Transfusion. N. G. Kirby. (*Lancet*, 1955, **268**, 594.) Machine oil containing sodium nitrite is being increasingly used and is widely obtainable. Such a preparation which after analysis was found to contain 36·5 per cent. of sodium nitrite, 7·5 per cent. of an emulsifying agent and 56 per cent. of water, was responsible for poisoning an 11-year old girl who had taken a mouthful. She was admitted to hospital 50 minutes later, and methæmoglobinæmia diagnosed. While oxygen was administered and a gastric lavage performed, an i.v. transfusion of group-O Rh-negative blood was started, a total of 1700 ml. being given. Following 48 hours in an oxygen tent, pyrexia and increased pulse rate lasting 4 days, and an affected blood picture, the patient improved sufficiently in 14 days to be discharged, with a blood picture within normal limits, and which remained so after 16 weeks. The author stresses the need for prompt action, in severe cases, preferably by exchange transfusion, and also the necessity of following up cases because of the danger of neutropenia and agranulocytosis. J. R. F.

Streptomycin, Rectal Absorption in Man. S. Carvalho and P. da Silva. (*Rev. Portugesa Farm.*, 1954, **4**, 225.) Following previous work, in which the

rectal absorption of streptomycin in rabbits was studied, the authors have administered 500 mg. of the antibiotic, as sulphate, to humans in a suppository base consisting of polyethylene glycols 1500–15 parts and 6000–75 parts. The antibiotic was detectable in the blood stream 15 minutes after administration, reaching a maximum concentration of 2 μg./ml. of serum in 1 hour and remained detectable up to 7 hours. The maximum level is considerably below that obtained by the intramuscular injection of the same quantity of antibiotic.

J. R. F.

Tricyclamol Chloride, Action of. P. Aylett and A. H. Douthwaite. (*Brit. med. J.*, 1955, **1**, 691.) This is a preliminary report on the effects of the new parasympathetic blocking drug, tricyclamol chloride (DL-*N*-methyl-3-*cyclo*-hexyl-3-hydroxy-3-phenylpropyl pyrrolidinium chloride). It is an odourless, crystalline substance, freely soluble in water, and may be given by mouth or intramuscular injection. The doses employed in the experiments varied from 25 to 100 mg. The drug was shown to have a marked effect in reducing the motility of the stomach and duodenum, and to a greater extent than was the case with hyoscyamine. This action may be of value in controlling the pain of peptic ulceration which is probably, at least in part, due to spasm. In a patient with gastroenterostomy and stomal ulcer quite severe pain was relieved after repeated oral doses of 50 mg. Tricyclamol had a less marked effect in reducing acidity of the gastric contents, but it prolonged the reduction of gastric acidity obtained by a dose of alkali (aluminium hydroxide gel). It is suggested that a combination of 100 mg. of tricyclamol chloride by mouth with a full dose of antacid might go some way towards overcoming the difficulty hitherto experienced in controlling nocturnal secretion in the treatment of duodenal ulcer. Side effects, including dryness of the mouth, dilated pupils, and blurring of print on reading, were observed in most of the patients; these effects seemed more pronounced after intramuscular injection than after oral use. S. L. W.

Uracil and Related Oxypyrimidines, Central Depressant Properties of. D. G. Wenzel and M. L. Keplinger. (*J. Amer. pharm. Ass., Sci. Ed.*, 1955, **44**, 56.) Uracil, thymine, 6-methyluracil and thiouracil were administered orally to mice in a dose of 2 millimole/kg. Thirty minutes later, 100 mg./kg. of hexobarbitone sodium was given intraperitoneally. Although these oxypyrimidines are devoid of hypnotic activity, they increased the sleeping time due to hexobarbitone. Similar results were obtained when the substances were injected intraperitoneally (1millimole/kg.) followed after 5 minutes by 100 mg./kg. of hexobarbitone sodium. Administered to mice in doses of 6 and 12 millimole/kg., followed after 40 minutes by 100 mg./kg. of leptazol (pentetrazol), the substances were ineffective in preventing the convulsions induced by leptazol. The compounds were however capable of preventing maximal electroshock seizures. The oral toxicity in mice was low, the LD50 varying from 3500 mg./kg. for thymine to more than 7500 for uracil and 6-methyluracil.

G. B.

Valmid, a Non-barbiturate Central Nervous System Depressant, a Study of the Effects of, in Humans. C. M. Gruber, K. G. Kohlstaedt, R. B. Moore and F. B. Peck, Jr. (*J. Pharmacol.*, 1954, **112**, 480.) Valmid (1-ethinyl:1-carbamyl *cyclo*hexane), administered in doses of 0·4 to 1·5 g. to patients in hospital, was an active hypnotic agent. The sedative action of 500 mg. was equal to that of 100 mg. of quinalbarbitone sodium, but the duration of action was about half of that of the barbiturate. No prolongation or intensification of the action of Valmid was observed in 2 patients with uræmia and cirrhosis.

In hypnotic doses the drug had no effect on respiration, heart rate or blood pressure in normal patients. G. P.

Veratrum Alkaloids, Mechanism of Vasomotor Action of. S. C. Wang, S. H. Ngai and R. G. Grossman. (*J. Pharmacol.*, 1955, **113**, 100.) A study has been made of the effects of veratrum alkaloids—Veriloid, protoveratrine, germitrine, neogermitrine, germerine, veratridine and veratramine—on the blood pressure of anæsthetised cats and dogs, to determine the extravagal sites of action. The alkaloids were injected intravenously, intra-arterially, or applied locally to the carotid sinus. To determine changes in the excitability of the medulla oblongata the central vasomotor mechanism was stimulated directly. In vagotomised animals moderate to severe hypotensive reactions were obtained with Veriloid, protoveratrine, germitrine, neogermitrine and germerine. During the hypotensive response the carotid sinus reflex was depressed or eliminated and the excitability of the medullary vasomotor centre was increased. The hypotensive response was not dependent on the activity of the carotid body, and it is suggested to be due to increased repetitive firing of the carotid sinus baroreceptors. Veratridine and veratramine depress the vasomotor centre and here it is believed that the carotid sinus baroreceptors play a secondary role in the hypotensive reaction. In all cases hypotension is mediated through inhibition of the sympathetic nervous system, no appreciable change in blood pressure being observed in chronically sympathectomised, cervical spinal animals or animals in which the sympathetic nerves have been blocked with Hydergine. Veratrum alkaloids had practically no direct action on the blood vessels. Veratramine caused a bradycardia on the denervated heart. Repeated doses of veratrum alkaloids only cause tachyphylaxis when the receptors are still under the influence of the alkaloids. G. F. S.

Vitamin K_1 and Water-soluble Vitamin K, Clinical Comparison of. J. R. Gamble, E. W. Dennis, W. W. Coon, P. Hodgson, P. W. Willis, J. A. MaCris and I. F. Duff. (*Arch. intern. Med.*, 1955, **95**, 52.) The prothrombin responses to water-soluble and to oil-soluble vitamin K preparations in patients under treatment with anticoagulants is compared. It is shown that oil-soluble vitamin K_1 (Mephyton) is more effective than any other agent now available in combating drug-induced hypoprothrombinæmia. In contrast, the water-soluble vitamin K preparations are unreliable and inconstant in effect. In most cases oil-soluble vitamin K_1 in doses as low as 1 to 5 mg. orally produces as satisfactory a response, in as short a time as 4 hours, as the large intravenous doses of water-soluble vitamin K usually recommended. This low dose has the advantage of permitting an early resumption of anticoagulant therapy, and no refractoriness was observed after using these small doses to the subsequent administration of anticoagulants administered orally. In the case of severe bleeding due to oral anticoagulants, intravenous vitamin K_1 in a dose of 10 to 50 mg. is recommended, in addition to whole blood or plasma transfusions, if the latter are necessary to combat shock; the smaller dose should be adequate when bleeding is moderate and resumption of therapy is planned. In hypoprothrombinæmia due to absorptive difficulties water-soluble vitamin K preparations or the oil-soluble vitamin K_1 appear to be equally effective, the latter in amounts as small as 5 mg. intravenously. In patients with jaundice of unknown ætiology a 50 mg. intravenous dose is recommended, and where there is poor initial response this dose may be repeated on successive days to produce a rise to safe prothrombin levels. No untoward effects have been observed from the use of this preparation. S. L. W.