# ABSTRACTS OF PAPERS PUBLISHED IN OTHER JOURNALS

## CHEMISTRY

### ALKALOIDS

***Veratrum album*, Hypotensive Alkaloids of.** W. L. Glen, G. S. Myers, R. Barber, P. Morozovitch and G. A. Grant. (*Nature, Lond.*, 1952, **170**, 932.) The isolation of two new hypotensive ester alkaloids from commercial samples of *Veratrum album* is reported; these alkaloids are named germitetrine and veratetrine. The crystalline fraction obtained by extraction from the drug was submitted to countercurrent distribution using benzene and 2 M acetate buffer at *p*H 5·5. Protoveratrine was isolated from tubes 17 to 24 and identified by its physical constants and by degradation experiments. Material recovered from tubes 10 to 15 crystallised from benzene to yield germitetrine, m.pt. 229 to 230° C.; $[\alpha]_D^{25°\,C.}$ –74° (1 per cent. in pyridine); $[\alpha]_D^{25°\,C.}$ –12° (1 per cent. in chloroform). Analytical data indicated an empirical formula $C_{41}H_{63}O_{14}N$ and equivalent weight 780. Its infra-red spectrum is characteristic and differs from the spectra of protoveratrine and veratetrine. Alkaline hydrolysis yielded the alkamine, germine and acetic acid (2 mol.), α-methylbutyric acid (1 mol.) and a third unidentified acid (*p*-phenylphenacyl ester m.pt. 163 to 164°). Estimation of volatile acid indicated that the unidentified acid was non-volatile. Tubes 0 to 9 from the countercurrent distribution experiment yielded veratetrine m.pt. 269° to 270° C. (decomp.) $[\alpha]_D^{26°\,C.}$ –32° (1 per cent. in pyridine); $[\alpha]_D^{27°\,C.}$ –6·8° (2 per cent. in chloroform). Analytical data indicated an empirical formula $C_{43}H_{64}O_{16}N$ and an equivalent weight of 839. Alkaline hydrolysis yielded *iso*protoveratrine, acetic acid, α-methylbutyric acid and an unidentified acid. J. B. S.

### ANALYTICAL

**Antihistamine Bases and their Salts, Potentiometric Titration Methods for.** L. J. Kleckner and A. Osol. (*J. Amer. pharm. Ass., Sci. Ed.*, 1952, **41**, 573.) A series of 8 antihistamine drugs was assayed (*a*) by adding sodium chloride and sodium hydroxide, extracting with ether, followed by evaporation of the solvent and direct or back-titration of the residue or (*b*) by titration in acetic acid solution with 0·1 N perchloric acid, mercuric acetate being added if necessary to eliminate halogen ions. Results by the perchloric acid method were as much as 1 per cent. higher than by extraction of the base and titration. The end-point in the non-aqueous titration was detected potentiometrically using glass and calomel electrodes, or by the use of 0·5 ml. of a 1 per cent. solution of crystal violet in glacial acetic acid as indicator. A standard solution of perchloric acid in dioxan gave a sharper end-point than the reagent prepared with glacial acetic acid. The solution in the best commercial grade of dioxan was stable over at least 10 weeks although a light yellow colour developed. Using other grades of dioxan, the solution became dark brown within 24 hours. Attention is drawn to the temperature coefficient of dioxan which may cause significant errors. Titration in the non-aqueous medium appears to be more satisfactory than the extraction procedure. G. B.

**Hydrastine, Determination of.** C. G. van Arkel and M. Meijst. (*Pharm. Weekbl.*, 1952, **87**, 853.) In the Netherlands official method for the determination of hydrastine in hydrastis rhizome and extract, the final solution, in ether-light

petroleum, is evaporated to small volume and, after standing, the solvent is poured off. The object of this is to remove berberine and canadine. Actually this liquor was found to contain a considerable quantity of hydrastine, and no berberine. Titrimetric determination of hydrastine also is inaccurate. Proposed new methods are as follows: (1) 3 g. of the powdered rhizome is shaken with 30 g. of ether and 2·5 ml. of 10 per cent. ammonia for 30 minutes, then treated with 3 ml. of water and filtered. The ethereal solution is shaken with 10 ml., then 3 times with 5 ml., of 1 per cent. hydrochloric acid. The filtered acid solution is made alkaline with 5 ml. of ammonia, and shaken out with an amount of ether equal to the weight of the ethereal solution. After the addition of 3 g. of tragacanth, the ethereal solution is filtered, 20 g. of the filtrate is evaporated to 5 ml., and the evaporation is completed by allowing to stand. The residue of hydrastine is dried at 100° C. and weighed. (2) 4 g. of liquid extract of hydrastis is boiled with 16 ml. of water until 8 g. remain, 4 ml. of 4N hydrochloric acid and water to 16 g. are added to the hot solution and, after 24 hours, 1 g. of talc is added and the mixture is filtered. To 10 g. of filtrate is added 1 ml. of ammonia, and the solution is shaken with 25 g. of ether. After the addition of 25 g. of light petroleum (b.pt. 65 to 80° C.) and 3 g. of tragacanth, the mixture is filtered. The filtrate is then treated as above. G. M.

**Phenols, Identification of, by Paper Partition Chromatography.** W. Chang R. L. Hossfield and W. M. Sandstrom. (*J. Amer. chem. Soc.*, 1952, **74** 5766.) Phenols can be successfully chromatographed using paper partition chromatography after coupling with diazotised sulphanilic acid to form phenylazobenzenesulphonic acid dyes. The migration coefficients for many phenols are recorded. A limitation of the method results from the fact that phenols which have a carbonyl function such as an aldehyde group *para* to the phenolic hydroxyl may react through replacement of the group by the entering azo group, thus destroying the identity of the original compound. Catechols could not be successfully chromatographed because of their sensitivity to oxidation. A. H. B.

**Polyvinylpyrrolidone Preparations, Evaluation of.** G. B. Levy, I. Caldas and D. Fergus. (*Analyt. Chem.*, 1952, **24**, 1799.) The evaluation of polyvinylpyrrolidone preparations is discussed in detail, the tests described being in addition to those specified in the U.S.P. XIV. The monomeric vinylpyrrolidone content should also be specified because of its relative toxicity; an aqueous solution containing the monomer is treated with sulphuric acid yielding an equivalent amount of acetaldehyde, which is then distilled and allowed to react with hydroxylamine hydrochloride; the liberated hydrochloric acid is determined volumetrically. With respect to the molecular weight, the range of average intrinsic viscocity (or K value) should be given; in addition, the upper and lower 10 per cent. of the material should fall within certain limits of intrinsic viscocity (or corresponding K value). Detailed methods are given for the various determinations proposed including the demineralisation of the solutions with ion-exchange resins prior to viscosity determinations. R. E. S.

## ORGANIC CHEMISTRY

***p*-Aminosalicyclic Acid, Decomposition of, by Heat.** V. G. Jensen and E. Jerslev. (*Dansk Tidsskr. Farm.*, 1952, **26**, 227.) The absorption of *m*-aminophenol, dissolved in water, is much less than that of *p*-aminosalicylic acid, and it is not possible to determine the former compound in the presence of a large quantity of *p*-aminosalicylic acid photometrically. Conditions are more

favourable at *p*H 1 (i.e. in 0·1N hydrochloric acid), where *m*-aminophenol shows a maximum at 271 mμ, while *p*-aminosalicylic acid shows a minimum at 255 mμ and a maximum at 300 mμ. By determining total absorptions at 271 and 300 mμ the concentrations (in mg./l.) of *p*-aminosalicylic acid (x) and of *m*-aminophenol (y) can be calculated from the following equations:

$$E_{271m\mu} = a_1x + b_1y,\ E_{300m\mu} = a_2x + b_2y$$

where $a_1$ and $a_2$ are the extinction coefficients (1 mg./l.) for *p*-aminosalicylic acid at 271 and 300 mμ respectively, and $b_1$ and $b_2$ the corresponding values for *m*-aminophenol. Values given are: $a_1 = 0{\cdot}01177$; $b_1 = 0{\cdot}01724$; $a_2 = 0{\cdot}03218$; $b_2 = 0$. After heating a solution of *p*-aminosalicylic acid at 100° C. for 30 minutes, decomposition is negligible at a *p*H above 7·5, but 15 per cent. at *p*H 6·0. The decomposition raises the *p*H, which retards the decomposition. Discolouration of solutions is most conspicuous in alkaline solutions, but is not proportional to the amount of decomposition. The addition of acid substances to prevent decomposition is not permissible, since it increases the formation of *m*-aminophenol. G. M.

# BIOCHEMISTRY

## GENERAL BIOCHEMISTRY

**Adrenocorticotrophic Hormone, Binding of Metal Ions by.** J. E. Carr, J. B. Conn and T. G. Wartman. (*Science*, 1952, **116**, 566.) A survey of the polarographic behaviour of a number of metal ions in solutions containing adrenocorticotrophic hormone led to the discovery that the hormone binds zinc and copper (II) ions in acid solution, and that a relationship exists between the extent of binding under certain fixed conditions and the adrenocorticotrophic activity as judged by rat assay. The zinc polarographic wave was chosen for study, and a standard procedure for measurement of the zinc-binding reaction adopted using numerous samples of the hormone (the potency of which had been determined by the hypophysectomised rat method). The sample was dissolved in the standard zinc solution at a concentration such that the diminution of the zinc wave lay between 10 to 50 per cent. and the solution polarographed in the voltage range − 0·8 to − 1·4 (*vs* SCE) and current range 5 μ amp. The observed diffusion current was read and entered into the calibration equation. No amino-acid was found to show any evidence of zinc binding under the conditions employed for the hormone, and the peptides L-prolyl-L-valine and glutathione gave negative results. However, salmine and dihydrostreptomycin bound zinc strongly. The only obvious common features of adrenocorticotrophic hormone, salmine and dihydrostreptomycin are (1) they are all cations under the conditions of study, and (2) they contain guanidine residues. A. H. B.

**17-Ketosteroid Excretion in Gout.** W. R. Butt and F. G. W. Marson. (*Brit. med. J.*, 1952, **2**, 1023.) Determinations of the 17-ketosteroid value of the urine were made in 33 gouty patients, using a polarographic method. Results showed no significant deviation from the normal values. The authors were unable to confirm that gout is characterised by low 17-ketosteroid excretion, as has been reported by other investigators. G. B.

**Vitamin $B_{12}$ Activity in Liver Injection, Stability of.** E. M. Stapert, E. B. Ferrer and L. Stubberfield. (*J. Amer. pharm. Ass. Sci. Ed.*, 1952, **41**, 587.) Liver injections, stored in filled sealed 10-ml. containers retained 85 per cent. of their vitamin $B_{12}$ potency for 10 months when stored at 5° C. or 24° C., or 76 per cent. when stored at 40° C. or 47° C. Storage in partially filled containers,

or exposure to air or oxygen caused a loss of 87·5 per cent. of the potency within three months. Variation of the amount of air present in a sealed container altered the stability of the product, but increasing the oxygen concentration of the air did not increase the rate of deterioration. Containers subjected to autoclaving showed a lag of 3 to 4 days, possibly due to depletion of the dissolved oxygen, after which deterioration continued as in the untreated samples. Exposure of the liver extracts to diffuse daylight did not cause appreciable deterioration in 7 days, although a loss of 15 per cent. of the potency was observed in samples subjected to intense incandescent illumination for 2 hours. In these experiments, microbiological assays using *L.leichmannii* were in good agreement with chemical assays. G. B.

**Vitamin $B_{12}$, Production by Actinomycetes.** A. P. Saunders, R. H. Otto and J. C. Sylvester. (*J. Bact.*, 1952, **66**, 725.) During studies on isolates of soil actinomycetes for antibiotic production a routine screening procedure was developed for the detection of vitamin $B_{12}$-producing strains. 90 cultures of actinomycetes were screened for vitamin $B_{12}$ production on a soy-bean meal medium fortified with cobalt. 4 of these cultures were found to produce significantly higher yields of the vitamin than those of the control culture of *Streptomyces griseus*. One of these characterised as *S. griseus* gave yields of approximately 1·0 $\mu$g./ml. and the 3 non-griseus strains gave yields of 1·63 to 1·84 $\mu$g./ml. Data on 14 *S. griseus* strains indicated a narrow range of vitamin $B_{12}$ production with these cultures and none of the cultures gave as high yields as the best non-griseus strains. Details of the method employed in the screening and results obtained are given. S. L. W.

## BIOCHEMICAL ANALYSIS

**Colouring Agents for Use in Disc-antibiotic Sensitivity Tests.** J. H. Bowie and J. C. Gould. (*J. clin. Path.*, 1952, **5**, 356.) The use of cellulose-fast dyes enables discs for antibiotic sensitivity tests to be coloured for identification purposes. Triphenylmethane and acridine dyes and indicators are not suitable since they have an antibacterial effect or change colour during the tests. Ford red (Clayton aniline tolamine pink), Ford yellow (durazol yellow I.C.I.G.R. 200), Ford blue (chlorazol sky-blue I.C.I.F.F. 200), Ford orange (durazol fast orange I.C.I.R. 150) and Ford scarlet (durazol scarlet I.C.I. 4B 150), used at a concentration of 2·5 mg./ml. render the discs recognisable over normal incubation periods with all the usual media, except MacConkey's medium. The dyes have no effect upon the antibiotic and *vice versa*, except for streptomycin which must be tested on uncoloured discs. Equal quantities of sterile double-strength solutions of antibiotic and dye may be mixed and used to impregnate filter paper discs which will retain their potency for several months when stored at 4° C. in the wet state. G. B.

**Cortisone-like Hormones in Urine, Chemical Estimation of.** C. L. Cope and B. Hurlock. (*Brit. med. J.*, 1952, **2**, 1020). Adrenal cortical hormones in urine probably exist mainly as sulphates and glucuronides, which have to be hydrolysed without destruction of the hormones, before they can be extracted. In a comparison of methods of hydrolysis and extraction, samples of urine, ranging from high to low content of active adrenal cortical hormone were treated (1) by acidification to *p*H 1 and allowing to stand for 24 hours before extraction 4 times with 15 per cent. of the volume of chloroform and (2) by adjustment to *p*H 4·5 with acetate buffer and treatment with 50 units of $\beta$-glucuronidase per ml. for 48 hours at 37° C. followed by extraction with three quantities of 15 per cent.

of the volume of chloroform. Extracts were assayed by the eosinophil count depression in mice. The β-glucuronidase method increased the yield by an average of 99 per cent. over the treatment at *p*H 1. Higher concentrations of β-glucuronidase are being tried in an attempt to increase the yield further. The Porter-Silber reaction which gives a yellow colour, maximum absorption at 410 mμ, by heating the hormone in solution with phenylhydrazine in sulphuric acid is suitable for a chemical assay of high sensitivity but cannot be applied directly to urine extracts because of the development of interfering pigments. These can be removed by paper chromatography. Urine extracts in methanol were submitted to paper chromatography using benzene/formamide, the first part of the chromatogram, containing all the active hormone being dried and eluted with methanol. The recovery was about 86 per cent. 1 ml. of the concentrated solution was used for the Porter-Silber reaction and 1 ml. for a sulphuric acid reagent blank. Results, calculated on 85 per cent. recovery in the chromatography, compared well with the results of biological assay of the urine extract, assuming that an error of 30 per cent. can be expected in the biological method.

G. B.

**Noradrenaline (Arterenol) in Adrenaline, Limit Test for.** M. E. Auerbach. (*Drug Standards*, 1952, **20**, 165.) Samples of adrenaline (epinephrine USP), may occasionally contain 15 per cent. or more of noradrenaline, and as the physiological responses to the two substances are not the same, the following limit test is suggested. Warm gently 50 mg. with 2 ml. of a 3 per cent. w/v solution of tartaric acid in pyridine until dissolved, cool and dilute to 50 ml. Place 4 ml. in a test-tube calibrated at 10 ml., dilute to 5 ml. with pyridine, add 0·5 ml. of naphthoquinone reagent (2 per cent. of β-naphthoquinone-4-sulphonate in dimethylformamide) and allow to stand for 10 minutes. Add 2 ml. of a 2·5 per cent. w/v solution of ascorbic acid in pyridine, dilute with pyridine to 10 ml. and allow to stand for 5 minutes. The purple colour, if any, should not be deeper than that of a standard colour prepared at the same time. For a limit of 5 per cent., the standard is prepared from 3·8 ml. of standard adrenaline solution (0·1 per cent. w/v) and 1 ml. of noradrenaline solution (0·2 per cent. w/v). The procedure may be made quantitative by setting up a graduated series of standard colours and comparing them with the sample under test in a photoelectric colorimeter with 540 mμ filter. The test depends on the reaction of β-naphthoquinone-4-sodium sulphonate with primary amines, which proceeds rapidly in pyridine. The absence of water and the presence of ascorbic acid reduce the formation of interfering coloured substances by oxidative side reactions. G. B.

**Progesterone and Pregnenolone, Separation and Quantitative Determination of.** H. Reich, S. J. Sanfilippo and K. F. Crane. (*J. biol. Chem.*, 1952, **198**, 713.) These 2 steroids were separated and quantitatively determined as follows. The sample to be analysed was evaporated to dryness. The residue was dissolved in ethanol and the two ketones converted into their respective 2:4-dinitrophenylhydrazones by treatment with excess of 2:4-dinitrophenylhydrazine solution at room temperature. The excess of dinitrophenylhydrazine was removed by oxidation with Benedict's reagent and the aqueous solution then extracted with chloroform. The chloroform extract was dried with anhydrous sodium sulphate, the solvent was removed, the residue was dissolved in hexane-benzene (1:1), and this solution chromatographed on alumina. Spectrophotometry was used to determine the amounts of the separated 2:4-dinitrophenylhydrazones. The method was applied to quantities of pregnenolone and progesterone as small as 5 μg. A. H. B.

**Serum Iron and Iron-binding Capacity, Micro-estimation of.** G. Davies, B. Levin and V. G. Oberholzer. (*J. clin. Path.*, 1952, **5**, 312.) For the determination of serum iron, 0·2 ml. of serum is added, drop by drop to 0·1 ml. of 6N hydrochloric acid and allowed to stand for 10 minutes, 0·2 ml. of 20 per cent. trichloracetic acid is added drop by drop, and the mixture allowed to stand for a further 10 minutes. To 0·37 ml. of the supernatant liquid, after centrifuging, 0·05 ml. of 12N ammonium hydroxide, 0·05 ml. of saturated solution of sodium acetate, 0·01 ml. of phenanthroline solution, 0·3 mg. of sodium hydrosulphite and water to produce 0·55 ml. are added. The colour is measured in a photoelectric colorimeter with a green filter (Ilford no. 604). In each batch of determinations a series of standard iron solutions and a reagent blank are included, and the iron content is read from a linear graph plotted from the readings for the standard solutions. Reagents and glassware must be free from iron. For the estimation of the total iron-binding capacity, 0·025 ml. of iron solution (50 $\mu$g./ml.), freshly reduced with ascorbic acid is added to 0·2 ml. of serum, to saturate the iron-binding $\beta_1$ globulin component. The excess of iron is allowed to react for 1 hour with 0·01 ml. of phenanthroline solution in the presence of 0·3 mg. of sodium hydrosulphite, and 0·2 ml. is added slowly to a mixture of 0·15 ml. of 6N hydrochloric acid and 0·1 ml. of water, liberating the iron from the iron-globulin compound, but not from the iron-phenanthroline complex. The determination is completed similarly to the serum-iron estimation. Hæmoglobin in amounts up to 140 mg./ml. of serum, equivalent to 1 per cent. hæmolysis of red corpuscles, will not affect the iron estimation provided that the serum is previously saturated with carbon monoxide. In normal adults, the average serum iron is higher in males than females, but there is no clear sex difference in iron-binding capacity. In hypochromic anæmia the percentage saturation and the serum iron are low, the iron-binding capacity being near the upper limit of the normal range. In hæmochromatosis, serum iron is high while the iron-binding capacity is near the lower limit of the normal range, the percentage saturation being about 100. Two cases of transfusion hæmosiderosis due to multiple transfusions for aplastic anæmia also showed approximately 100 per cent. saturation. G. B.

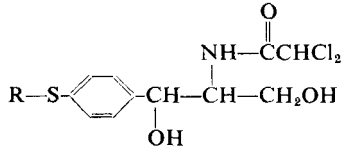
**Uric Acid in Plasma, Determination of.** J. M. Johnstone. (*J. clin. Path*, 1952, **5**, 317). The following method of determination may be used. 1 ml. of plasma is treated with 7 ml. of water, 1 ml. of sodium tungstate solution (10 per cent.) and 1 ml. of 0·66 N sulphuric acid. The mixture is allowed to stand for 20 to 30 minutes and centrifuged. To 4 ml. of the supernatant liquid 0·8 ml. each of lithium chloride solution (0·75 per cent.) and silver nitrate solution (2·9 per cent.) are added. The liquid is again centrifuged and to 3·5 ml. of the supernatant fluid, 2 ml. of a 50 per cent. solution of urea, 2 ml. of 12 per cent. solution of sodium cyanide and 1 ml. of phosphotungstic acid solution are added. The solution is diluted to 15 ml. and the colour measured after 45 to 50 minutes, in a photoelectric colorimeter with a red filter (Ilford no. 608). A blank test to determine the non-uric acid reacting substances is performed by incubating plasma with water and uricase extract for 2 hours at 45° C. and then developing the colour as described above. A further blank test is done on the uricase incubated with water for 2 hours at 45° C. and submitted to the colour reaction. The colour intensity after correction for colour due to non-uric acid interfering substances is read against a calibration curve prepared by plotting the colour intensities obtained with standard uric acid solutions. No correlation was found between total uric acid and non-uric acid reacting substances. In gout, all raised

uric acid values were accompanied by normal amounts of interfering substances, but in many uræmic patients, high values for uric acid were accompanied by high figures for non-uric acid reacting substances. The average total plasma uric acid value in normal individuals was found to be 4·14 ± 0·16 mg./100 ml.

G. B.

## CHEMOTHERAPY

**2-Acylamino-1-(4-hydrocarbonylsulfonylphenyl)-1 : 3-propanediols and Related Compounds as Antibacterial Agents.** R. A. Cutler, R. J. Stenger and C. M. Suter. (*J. Amer. chem. Soc.*, 1952, **74**, 5475.) The preparation of a number of racemic *threo*-2-dichloroacetamido-1-(4-hydrocarbonylmercaptophenyl)-1:3 propanediols (I)



(I)

and their corresponding sulphones where R = $CH_3$—; $C_2H_5$—; *n*-$C_3H_7$—, *n*-$C_4H_9$—, $C_6H_5$—, $C_6H_5CH_2$—are described. The methyl analogues (R = $CH_3$) in both the sulphide and sulphone series exhibited outstanding antibacterial action against a number of pathogenic organisms using *in vitro* tests. Lengthening of the chain attached to the sulphur atom resulted in a marked decrease in activity in both series. Reduced activity resulted by the replacement of the dichloroacetyl group by the acetyl group. The methyl analogues (R = $CH_3$) in both the sulphide and sulphone were also prepared in their optically active forms.

A. H. B.

***p*-Aminobenzoic Acid and Dimethyldiaminobenzene, Aggregate Analogues of.** D. W. Woolley. (*J. Amer. chem. Soc.*, 1952, **74**, 5450.) The name "aggregate analogues" was given to the new compounds prepared because they were constructed by union of appropriate analogues of two distinct essential metabolites, viz. *p*-aminobenzoic acid and 1:2-dimethyl-4:5-diaminobenzene. These compounds were conceived as a means of realising new pharmacological agents of high potency, and with a type of action which would not be antagonised by the metabolites to which they were structurally or functionally related. They were tested as inhibitors of the growth of *Staphylococcus aureus* and two kinds of outstanding biological properties were observed: (1) high antibacterial potency in some of the compounds, and (2) difficulty, or inability of the structurally related metabolites, and even of the products of the inhibited reactions, to overcome the antibacterial effect. The toxicity of these substances in mice was either low or undetectable. The concept of how these aggregates function biologically is essentially that of a multiple block in a series of connected and co-ordinated reactions in a vital process of the cell. Even though one half of the aggregate may form a reversible combination with the one active, enzymic centre, it is still anchored by its other half to the second enzyme which is anatomically and spatially oriented with the first.

A. H. B.

**Analgesics, Newer Synthetic.** P. W. Nathan. (*Brit. med. J.*, 1952, **2**, 903.) Doses of analgesic drugs were administered to 75 patients who had chronic pain, constant over a few weeks and who were able to keep pain charts. Headaches and painful complaints such as colic or peptic ulcer which are better treated with spasmolytic drugs, were excluded from the investigation. From the results, examined statistically, 12 mg. of methadone, 125 mg. of pethidine, 10 mg. of phenadoxone by injection or 50 mg. orally were equiactive with 16 mg. of morphine. Höchst 10581 (DL-6-morpholino-4: 4-diphenylhexan-3-one hydrochloride) was similar to phenadoxone, but had a longer analgesic effect. Methadone, by injection, acted longer than when given by mouth. No single drug proved constantly more toxic than the others; each caused toxic symptoms such as dulling of the intellectual activity, anorexia, dizziness, nausea, vomiting or sweating in some patients. There was no evidence that methadone affects a patient's alertness less than morphine. The following suggested single doses are based on considerations of analgesic effectiveness and side effects:—morphine, 11 to 65 mg.; methadone, 5 to 30 mg. (with slight pain, 2·5 mg. may be enough); pethidine, 50 to 250 mg., and phenadoxone, 10 mg. by injection (20 mg. may be dangerous). Phenadoxone and Höchst 10581, given orally were unreliable and rarely effective. Addiction did not develop in any patient after a pain-relieving operation had made the use of the drugs unnecessary. G. B.

**Antithyroid Activity of some Compounds that Inhibit Peroxidase.** I. N. Rosenberg. (*Science*, 1952, **116**, 503.) A number of phenol and aniline derivatives were tested for antithyroid activity in rats. The substance under test, dissolved in water or dilute ethanol was injected subcutaneously, and 6–8 $\mu$c. of $^{131}$I was given intraperitoneally 1 hour later. After 4 hours, the animals were killed, the thyroids removed, dissolved in hot sodium hydroxide solution, and a sample submitted to X-ray counting. The results, expressed as a percentage of the iodine uptake in untreated controls showed that resorcinol, phloroglucinol, *m*-phenylenediamine, *m*-aminophenol, 4-aminosalicylic acid, aniline and *o*-, *m*-, and *p*-toluidine have a marked antithyroid activity. These substances also showed marked inhibition of peroxidase. Pyrogallol, *o*- and *p*-phenylenediamine, *p*-aminophenol and 5-aminosalicylic acid were inactive against thyroid and peroxidase. Experiments with animals pretreated with propylthiouracil indicated that the ratio of thyroid to serum iodine is not affected by the administration of phloroglucinol or aniline. These substances appear to act by inhibiting the organic binding of iodine by the thyroid without affecting the iodine concentrating mechanism. Most classes of antithyroid substances are either competitive substrates (thiocarbonamides) or inhibitors (sulphonamides, anilines and polyphenols) of peroxidase. In the polyhydric phenols and amines the *meta*-configuration appears particularly active against both thyroid and peroxidase. G. B.

# PHARMACY

## DISPENSING

**Glucose Solutions, Discolouration of, on Sterilisation.** W. Völksen. (*Arch. Pharm. Berl.*, 1952, **285**, 392.) The discolouration of strong solutions of glucose, which results from sterilisation, is affected by the purity of the sample, the temperature and duration of sterilisation, the alkali content of the glass, the presence of oxygen, and in particular by the *p*H of the solution. Discolouration of the solution after heating at 120° C. can be suppressed by adjusting the *p*H to about 3·5 by the addition of hydrochloric acid. Such weakly acid solutions may

be used for intravenous injection without any side effects, since the buffer capacity of the blood is quite sufficient to deal with such small amounts of acid.

G. M.

## NOTES AND FORMULÆ

**Iodopanoic Acid (Telepaque).** (*New and Nonofficial Remedies*; *J. Amer. med. Ass.*, 1952, **150**, 795.) Iodopanoic acid is β-(3-amino-2: 4: 6-tri-iodophenyl)-α-ethylpropionic acid and occurs as a cream-coloured, tasteless, faintly aromatic powder which darkens on exposure to light; m.pt. 152° to 158° C., soluble in acetone, ethanol and dilute alkalis, insoluble in water. A 0·00075 per cent. ethanolic solution exhibits ultra-violet absorption maxima at about 230 mμ [$E^{1\%}_{1\,cm.}$, about 667] and at about 315 mμ. It loses not more than 1·0 per cent. of its weight when dried at 105° C. for 30 minutes, and yields not more than 0·1 per cent. of sulphated ash. The content of iodopanoic acid is 95·0 to 105·0 per cent., calculated from the absorption at 230 mμ of a 0.00075 per cent. ethanolic solution, and 96·0 to 104·0 per cent. when determined by fusing with potassium nitrate and sodium hydroxide and estimating the resulting iodide with silver nitrate. Iodopanoic acid is used as a contrast medium in radiography.

G. R. K.

**Methantheline Bromide (Banthine Bromide).** (*New and Nonofficial Remedies*; *J. Amer. med. Ass.*, 1952, **150**, 590.) Methantheline bromide is β-diethylmethylaminoethyl 9-xanthenecarboxylate bromide and occurs as a white or nearly white, bitter, odourless, microcrystalline powder, m.pt. 172° to 177° C., soluble in water and ethanol and almost insoluble in ether; a 2 per cent. solution has a *p*H of 5·0 to 5·5. The precipitate obtained by heating a solution with sodium hydroxide for 2 minutes and acidifying the hot solution with hydrochloric acid melts at 218° to 223° C. Methantheline bromide gives a bright yellow to orange solution with sulphuric acid. A 0·005 per cent. ethanolic solution exhibits ultra-violet absorption maxima at about 2460 Å [$E^{1\%}_{1\,cm.}$, about 135] and at 2820 Å [$E^{1\%}_{1\,cm.}$, about 69], and minima at about 2400 Å and 2700 Å; the ratio of the absorptions at 2460 Å and 2820 Å is 1·85 to 2·05. When dried in a vacuum desiccator over phosphorus pentoxide for 24 hours, it loses not more than 0·5 per cent. of its weight. It yields not more than 0·1 per cent. of sulphated ash, and contains 96·5 to 103·0 per cent. of methantheline bromide (determined by measuring the absorption of a 0·005 per cent. ethanolic solution at 2820 Å), 18·4 to 19·2 per cent. of bromide, and 3·28 to 3·40 per cent. of nitrogen.

G. R. K.

**Methorphinan Hydrobromide (Dromoran Hydrobromide).** (*New and Nonofficial Remedies*; *J. Amer. med. Ass.*, 1952, **150**, 488.) Methorphinan hydrobromide is 3-hydroxy-*N*-methylmorphinan and occurs as a bitter fluffy white crystalline powder, m.pt. 195° to 197° C., soluble in ethanol, sparingly soluble in water, and slightly soluble in chloroform and ether; a 2 per cent. solution is clear and almost colourless and has *p*H 5·0 to 5·6. It gives a greenish-yellow colour with a solution of sodium molybdate in sulphuric acid and a brownish-yellow colour with a mixture of formaldehyde and sulphuric acid, which becomes greenish-yellow on dilution with water. A 0·005 per cent. solution in ethanol exhibits ultra-violet absorption maxima at about 2210 Å [$E^{1\%}_{1\,cm.}$, about 190] and 2820 Å [$E^{1\%}_{1\,cm.}$, about 65] and a minimum at about 2450 Å. Methorphinan hydrobromide loses not more than 3·0 per cent. of its weight when dried at 120° C. for 4 hours and yields not more than 0·1 per cent. of sulphated ash. It contains 98·5 to 101·5 per cent. of methorphinan hydrobromide and is assayed

by extracting an alkaline solution with a mixture of chloroform and ether, re-extracting with hydrochloric acid and back-titrating the excess of acid. Methorphinan hydrobromide is a synthetic analgesic. G. R. K.

## PHARMACOGNOSY

***Claviceps purpurea*, Growth and Nutrition in Submerged Culture.** V. E. Tyler, Jnr., and A. E. Schwarting. (*J. Amer. pharm. Ass. Sci. Ed.*, 1952, **41**, 590.) A 100-ml. quantity of nutrient solution containing carbon and nitrogen sources was placed in a 500-ml. flask, autoclaved and inoculated with *C. purpurea*. The flask was placed on a reciprocating shaking machine making 150 excursions per minute for 6 to 8 days at room temperature to obtain maximum growth of mycelium. The yield was 1·48 g. dry weight of growth in a suitable medium. Mannitol and lævulose appeared to be the best carbon sources, although glucose could also be used. Maltose, lactose and galactose were poor sources of carbon for this purpose. Casein hydrolysate and soy hydrolysate were the best nitrogen sources, followed by yeast extract, corn steep solids and peptone. *p*H determinations carried out during the growth of *C. purpurea* in a medium containing 1 per cent. of glucose suggested that the carbohydrate was converted into an organic acid (*p*H decrease) which was then metabolised with an increase of *p*H to about 7, after which the organism began to undergo autolysis, releasing basic substances and giving rise to a further increase in *p*H. Thus *p*H observations made it possible to estimate approximately the time of maximum growth in any given medium. Great differences in growth rates, appearance and pigment formation were observed as a result of strain differences in *C. purpurea*. G. B.

## PHARMACOLOGY AND THERAPEUTICS

**Analgesics, a Method for Testing, in Mice.** R. Singh Grewal. (*Brit. J. Pharmacol.*, 1952, **7**, 433.) A method is described for testing analgesics in mice using quantal responses to electric shocks applied to the tail. There was a linear relationship between the log. dose and the percentage of mice showing analgesia, and the regression lines obtained for morphine, amidone, pethidine and phenadoxone were parallel. The relative activities (with morphine as 1) were, for amidone 1·25; phenadoxone 3·56 and pethidine 0·33. Phenazone, even in large doses, showed only slight analgesic activity. G. F. S.

**Antiheparin Dyes, Effect on the Isolated Ileum and Uterus.** J. L. Leitch and T. J. Haley. (*J. Amer. pharm. Ass., Sci. Ed.*, 1952, **41**, 559.) The pharmacological properties of 4 antiheparin dyes, toluidine blue, azure A, neutral red, and neutral violet on isolated organs were investigated. Quantitative results obtained with the guinea-pig ileum indicate that these dyes have about 1/10,000 the potency of atropine in counteracting acetylcholine spasm. They have a less potent antimuscarinic activity than atropine, but with the exception of neutral violet, are equivalent in their antinicotinic effects. The apparent correlation between chemical structure and pharmacological effect is considered. A. H. B.

**Chlorinated Phenols, Acute Toxicity of.** J. M. Joseph. (*J. Amer. pharm. Ass. Sci. Ed.*, 1952, **41**, 595.) Toxicity was determined by the intraperitoneal injection of pure liquid methyl chlorothymol (2-*tert*.-butyl-4-chloro-5-methylphenol) and of an aqueous suspension of fine crystals of *p*-chloro-*m*-xylenol into albino mice. For methyl chlorothymol the MLD and LD 50 were 0·75 g./25 g. and for *p*-chloro-*m*-xylenol the MLD was 3·0 g./25 g., the LD 50 being calculated

as 2·88 g./25 g. It is concluded that the compounds may be considered safe for use in germicidal preparations and for the preservation of pharmaceutical products. G. B.

**Colchicine, General Pharmacology of.** F. C. Ferguson. (*J. Pharmacol.* 1952, **106**, 261.) Toxicological effects in rats were characterised by a long delay between the administration of colchicine and the appearance of effects. The intravenous LD 50 for rats was about 1·7 mg./kg., and death was delayed by up to two weeks. Chronic toxicity tests showed that a daily intraperitoneal injection of 0·4 mg./kg. depressed growth and with 1·6 mg./kg. 35 per cent. of the rats died by the fourth day. Cats were more sensitive, 0·25 mg./kg. being a toxic dose intravenously. Acute actions of colchicine in both species were due to severe and prolonged gastro-intestinal disturbances neurogenic in origin. Other actions of colchicine showed no significant effects on respiration in doses up to 10 mg./kg. and minor effects on the heart. A dose of 5 mg. caused a slow rise in blood pressure and an increase in the peripheral arterial resistance due to medullary stimulation since the effects were prevented by prior transection of the upper cervical cord, but not by supra-tentorial transection of the brain stem. The excitatory effects of sympathomimetic drugs on the circulation and nictitating membrane were potentiated by colchicine. Intra-arterial administration of colchicine in doses up to 2 mg./kg. had no immediate effect on the gastrocnemius preparation subjected to both direct and indirect stimulation, nor were the effects of intra-arterial injections of curare, potassium and acetylcholine changed. Of particular interest was an extreme atrophy of the leg muscles in cats chronically poisoned by a daily dose of colchicine. Affected muscles showed abnormal responses to acetylcholine and potassium, resembling those seen after chronic denervation, although they responded in a normal fashion to indirect nerve stimulation but with a reduced contraction. The authors emphasise that colchicine possesses many pharmacological actions the mechanisms of which are largely unknown. G. F. S.

**Ethyl Biscoumacetate (Tromexan), Pharmacology of.** B. B. Brodie, M. Weimer, J. J. Burns, G. Simson and E. K. Yale. (*J. Pharmacol.*, 1952, **106**, 453.) Ethyl biscoumacetate like dicoumarol inhibits the clotting of blood, but it has a quicker onset of action and is less persistent when the drug is discontinued. It may be estimated in biological material by extraction with heptane containing *iso*amyl alcohol, re-extraction with alkali and measuring spectrophotometrically at 310 mμ. Studies in man showed ethyl biscoumacetate to disappear rapidly from the plasma following intravenous injection, before the prothrombin response became evident. Since it was only excreted in the urine as a metabolic product there must be a rapid rate of biotransformation. Biotransformation depended on the individual and the dose, and is much slower with dicoumarol. Oral administration showed the drug to be rapidly and completely absorbed from the gastro-intestinal tract, whereas with dicoumarol absorption is slow and sometimes incomplete. Repeated daily doses showed no cumulation; even after 6 hours following a high dose it was not detectable in the plasma. The prothrombin response is, however, cumulative, and reaches a plateau after several days of treatment. Wide variations occur in the individual response to this drug and sudden unpredictable changes in prothrombin time frequently occur in subjects receiving regular daily doses. Correction of these changes by readjustment of the dose is often difficult. G. F. S.

**Hetrazan, Control of Filariasis with.** I. A. McGregor, F. Hawking and D. A. Smith. (*Brit. med. J.*, 1952, **2**, 908.) Of 603 persons in a Gambian village,

220 were found to carry microfilaria of *Wuchereria bancrofti* and 203, *Acanthocheilonema perstans*. Five doses of diethylcarbamazine citrate (hetrazan), 5 mg. of base/kg. were administered. After 10 months, 64 per cent. of the persons were free from microfilariæ of *W. bancrofti*, the total microfilariæ being reduced by 94 per cent. Most of the infected persons had so few microfilariæ that it would have been unlikely for a mosquito to become infected. *A. perstans* was eliminated from the blood of 72 per cent. of those treated. Unpleasant side-effects, reported by 25 per cent. of those treated made it difficult to persuade them to take the later doses of diethylcarbamazine. Such effects may have been due to direct action of the drug (nausea), allergic reaction (fever, malaise) or to cellular reaction round a dying worm (swellings). Cough and chest pain were also reported. The toxic effects and high cost of diethylcarbamazine seriously prejudice the chances of its successful use in mass treatment in areas such as this, where less than 1 per cent. of filarial sequelæ are seen and people are not aware of the disease. G. B.

**Hexamethonium Bromide and its Homologues, Hypotensive Actions of.** F. H. Smirk. (*Lancet*, 1952, **263**, 1002.) Hexamethonium bromide, Ciba 9295 (*NNN'*, *N'*-3-pentamethyl-*NN'*-diethyl-3-azapentylene (1:5)-diammonium bromide) and M. and B. 1863 (hexamethylene bisethyldimethylammonium bromide) were administered to patients by subcutaneous injection. The drugs were qualitatively similar in reducing blood pressure, approximately equal falls being produced by 7 mg. of M. and B. 1863, 15 mg. of hexamethonium bromide and 17 mg. of Ciba 9295. When given orally, 10 or more times the subcutaneous dose was required, there being no great difference between these substances as regards the proportion absorbed. The administration of any of these compounds induced toleration to all of them. Toleration increased for weeks or months during continuous administration of the drug, until ordinarily 6 to 12 times the initial effective dose was required to produce the same hypotensive effect. The degree of toleration differed widely between patients. In some cases of hypertension, M. and B. 1863 was preferable to hexamethonium bromide, side effects being less pronounced. No adverse permanent tissue damage has been observed. There was little evidence of toxicity, other than the temporary form caused by overdosage. G. B.

**Histamine, Antihistamines and Hypnotic Drugs, Synergism between.** J. L. Ambrus, C. M. Ambrus, C. A. Leonard, C. E. Moser and J. W. E. Harrisson. (*J. Amer. pharm. Ass. Sci. Ed.*, 1952, **41**, 606.) The administration of histamine or of antihistamine drugs was found to prolong the period of sleep induced in mice by an intraperitoneal dose of 100 mg./kg. of hexobarbitone. In these experiments the sleeping time was taken as the interval between the injection of the barbiturate and the wakening time when the animal turned over spontaneously into the normal position but continued to sleep. A considerable prolongation of the sleeping time was observed with phenindamine (thephorin) which is reported to have a minimal sedative action of its own, or even a cerebral stimulating effect. This phenomenon cannot therefore be used as a test for the sedative side-effects of the antihistamines. The drugs also showed synergism with ether vapour administered rapidly to mice by means of a special apparatus. It is suggested that administration of antihistamines during ether anæsthesia may serve to decrease the dose of ether required, to decrease the mucous secretion, salivation, post-anæsthetic nausea and vomiting, to antagonise the possible effects of histamine and acetylcholine which may be liberated during surgery and to decrease cellular and capillary permeability, thus combating post-operative hæmorrhage and shock. G. B.

**Histamine, Release by Pethidine, Atropine, Quinine and Other Drugs.** M. Schacter. (*Brit. J. Pharmacol.*, 1952, **7**, 646). Experiments on the perfused isolated skin of the cat have shown that pethidine, atropine, quinine, tolazoline, neoarsphenamine and bile salts release histamine in this order of effectiveness. Pethidine and atropine also released histamine from the perfused isolated dog skin preparation. Intra-arterial injection into the aorta of eviscerated anæsthetised cats, through a cannula tied into the renal artery, showed that pethidine, atropine, and quinine raised the plasma histamine, while tolazoline, neoarsphenamine and bile salts, even in large doses, had no effect. Both pethidine and atropine also caused an increase in plasma histamine concentrations on intravenous injection in the cat, but the high doses required also produced severe toxic effects. The possible significance of these findings to observations of cutaneous drug reactions in humans is discussed. G. F. S.

**Hypotensive Drugs, Prolongation of the Action.** F. H. Smirk. (*Lancet*, 1952, **263**, 695.) Although the best available control of blood pressure in hypertensive patients is often obtained with aqueous injections of hexamethonium bromide, thrice daily, wide fluctuations in blood pressure occur in the intervals between the doses. Attempts were made to retard the effect of hexamethonium bromide or hexamethylene bisethyldimethylammonium bromide (M. and B. 1863) by the addition of adrenaline hydrochloride or mucate, ephedrine hydrochloride-polyvinylpyrrolidone or dextran to the solution to be injected The addition of 25 per cent. of polyvinylpyrrolidone or 20 per cent. of dextran (mol. wt. 20,000) prolonged the action of hexamethylene bisethyldimethylammonium bromide from 5 to 7 hours and further retardation was achieved by the addition of 0·05 per cent. of ephedrine hydrochloride. When using the slowly absorbed preparations it is necessary to increase the dosage by at least 30 per cent. over that required with simple aqueous injections. Oral administration of hexamethonium bromide at the time when the blood pressure is due to rise may sometimes prolong the hypotensive effect. G. B.

**Iron Salts, Therapeutic Response of Secondary Anæmias to.** D. Haler. (*Brit. med. J.*, 1952, **2**, 1241.) A series of 44 patients with anæmia following postpartum hæmorrhage, normal delivery or illness was selected at random and organic or inorganic preparations of iron were given to alternate cases. The organic preparation contained ferrous gluconate with aneurine hydrochloride, nicotinamide, riboflavine and black currant syrup providing a daily intake of 105 mg. of iron. Inorganic preparations used included ferrous sulphate, dialysed iron and saccharated iron (intravenous) with supplementary vitamins when necessary, providing 180 mg. of iron per day. The group treated with inorganic preparations showed a mean daily increase of 1·02 per cent. of hæmoglobin and an iron utilisation coefficient of 18·1, whereas in the group treated with an organic preparation the figures were 1·49 and 28·3. The hæmoglobin value reached normal limits within about 21·7 days in the inorganic, and 17·8 days, in the organic group. Ferrous gluconate seemed to produce a more satisfactory hæmoglobin response within a shorter time than ferrous sulphate. 25 per cent. of outpatients treated with ferrous sulphate tablets discontinued the treatment because of gastric side-effects. G. B.

**Isoniazid in Treatment of Renal Tuberculosis.** J. K. Lattimer. (*J. Amer. med. Ass.*, 1952, **150**, 981.) Isoniazid effects a gradual improvement in the cystoscopic appearance in tuberculous cystitis and is especially useful in streptomycin-resistant patients. It has certain disadvantages such as the development

of drug resistance by the infecting organism, and the fact that in uræmic patients the drug will accumulate in the blood and may reach a level at which hyperreflexia, muscle-twitching, spasm of the sphincters and convulsions occur. A raised prothrombin time, precluding surgery, was observed in some patients even when blood levels were normal. Frequent determinations of the blood levels are desirable and the sensitivity of the infecting tubercle bacilli should be determined as a guide to dosage. A daily quantity of 3 mg./kg. of body weight, in 2 doses, gives about 1 to 2 mg./ml. of blood which is adequate for most patients and non-toxic. Resistance may develop in 2 to 8 weeks when the drug is used alone; intermittent administration, perhaps in conjunction with streptomycin, may prove desirable. Liver damage must be watched for in patients treated with isoniazid for more than 6 months. The mode of action of isoniazid appears to differ from that of *p*-aminosalicylic acid or streptomycin and a combination of all these drugs may eventually be found to increase their effectiveness and to defer the development of drug resistance. A combination of isoniazid, 150 mg. twice daily by mouth, and streptomycin, 1 g. twice weekly, is being evaluated. H. T. B.

**L-Methorphinan as a Supplement to Nitrous Oxide and Oxygen Anæsthesia.** A. K. Brown. (*Brit. med. J.*, 1952, **2**, 1331.) The effects were investigated in a series of 100 patients, all of whom were undergoing major surgery. Anæsthesia was induced with thiopentone, maintained with nitrous oxide and oxygen, and an injection of L-methorphinan given as soon as the effect of the thiopentone on respiration was wearing off and further injections were given as required. The results of the trial were compared with those obtained in an earlier series of 100 cases in which pethidine was used. It was concluded that L-methorphinan is a powerful analgesic drug with a long action and its intravenous administration does not result in any untoward reactions. By the intravenous route it is a satisfactory adjuvant to nitrous oxide and oxygen anæsthesia, when it behaves in a similar fashion to pethidine. A. H. B.

**L-Methorphinan (L-Dromoran), Actions and Uses of.** A. J. Glazebrook. (*Brit. med. J.*, 1952, **2**, 1328.) A summary of the results of clinical trials confined to the relief of pain in patients in their homes and in hospital wards is given, and no method of evaluation involving the production of pain by mechanical or other methods was attempted. The most useful first dose to employ was 1·5 to 2 mg., but severe cases required the initial trial dose to be increased to 4 mg. L-Methorphinan failed to relieve pain in only 16 of the 200 cases treated (8 per cent.); and afforded slight easement in 25 cases (12·5 per cent.). A gratifying analgesia was produced in the other 159 cases (79·5 per cent.), and many admitted to a deeper and more profound relief than could be obtained with morphine injections. It is a longer-acting analgesic than morphine and can be given by mouth. A striking characteristic is its ability to produce cheerfulness in pain-depressed patients the morning after an evening dose. Patients who do not tolerate morphine are likely to exhibit similar symptoms with L-Methorphinan, although its smaller effective dosage may enable it to be used in these cases. It is not a hypnotic, and it is unwise to prescribe it with a barbiturate. It should not be used in cases of colic; while it will relieve pain it will induce smooth-muscle spasm lasting up to 2 hours after its administration. It is not so useful as codeine in the relief of painful cough, and is not so good as morphine in allaying extreme anxiety and restlessness when pain is not a feature. "L-Methorphinan has one prime function, the relief of pain, and for this purpose may be found superior to morphine." A. H. B.

**Phenylethylacetylurea, Pharmacology of.** P. Gold, E. Frommel, C. Radouco, G. Greder, D. Melkonian, R. Della Santa, S. Radouco, F. Vallette and M. Ducommun. (*Arch. int. pharmacodyn*, 1952, **91**, 437.) *In vivo* tests indicated that phenylethylacetylurea and substance M551 (a mixture of five parts of phenylethylacetylurea and one part of phenylacetylurea) were effective anticonvulsants, protecting animals against the convulsive effects of strychnine, leptazol, nikethamide and electric shocks. Anticonvulsive doses were not accompanied by sleepiness, but rather by a slight excitation of the animal. The maximum anticonvulsive effect occurred 3 to 5 hours after administration and there was no evidence of accumulation. Phenylethylacetylurea and M 551 exhibited an anticholinergic and neurovegetative action in experiments with the isolated guinea-pig intestine and in *in vivo* tests in guinea-pigs treated with an ærosol of acetylcholine. The substances were shown to act directly on smooth muscle and as mild histamine antagonists. They did not affect the respiration (rabbit), arterial pressure (rabbit, dog), cardiac rhythm or body temperature (guinea-pig). Anticonvulsant doses had no effect on the blood sugar, calcium and inorganic phosphorus levels. Large doses continued over a period of 12 weeks caused no alteration in the red and white cells and blood platelets, and in the myelograms of the animals. Subsequent histological examination showed that phenylethylacetylurea had no harmful effect on the liver or kidneys, but that M 551 in high doses was slightly toxic to liver because of its phenylacetylurea content. G. B.

**Salicylate, Respiratory Effects of.** J. B. Cochran. (*Brit. med. J.*, 1952, **2**, 964.) Experiments were performed in two healthy subjects and one rheumatoid patient treated with 10 g. of sodium salicylate dissolved in 400 ml. of water and administered by intravenous drip over 3 to 4 hours, and in 3 subacute rheumatic patients, given 1½ to 2 g. of aspirin five times daily. A closed-circuit Knipping-type spirometer was used to measure oxygen consumption, carbon dioxide output and depth and rate of respiration. Control tracings were made prior to salicylate treatment, and then 10-minute spirometer tracings were made at ½-hourly intervals. In 3 healthy controls, who received no salicylate, oxygen consumption and carbon dioxide output remained fairly constant throughout the day, but administration of salicylate was followed by a progressive and marked increase in oxygen consumption accompanied by a smaller increase in carbon dioxide output, i.e., the respiratory quotient decreased. The drug also increased the rate of respiration and the tidal volume. It is suggested that the marked increase in oxygen consumption may be of importance in the therapeutic action of the drug. G. B.

**Terramycin in the Treatment of Pneumonia in Children.** O. D. Fisher and C. D. Whitfield. (*Brit. med. J.*, 1952, **2**, 864.) In 63 cases of pneumonia in children, treatment with terramycin (44 mg./kg./day) was compared with the "standard treatment" consisting of sulphadimidine (0·5 g. every 4 hours) and 300,000 Units of procaine penicillin G injected intramuscularly every 12 hours. Dosage in the standard treatment is reduced for patients under 3 years. Recovery, assessed by duration of fever, average stay in hospital, development of complications and mortality showed no advantage for terramycin over the standard treatment, and there was a greater incidence of delayed resolution in the terramycin group. The use of terramycin avoids giving injections and precludes the possibility of toxic renal and hæmatological effects due to the sulphonamide, but in some cases a thrush infection of the mouth may develop. It is concluded that the combination of penicillin and sulphonamide remains the most satisfactory treatment. G. B.

**1-(*O*-Toluoxy)-2:3-bis-(2:2:2-trichloro-l-hydroxyethoxy) propane, Pharmacological Characteristics of.** J. F. Reinhard, E. T. Kimura and J. V. Scudi. (*J. Pharmacol.*, 1952, **106**, 444.) This compound is a non-barbiturate central nervous system depressant of low toxicity. Hypnotic activity was determined in mice as the minimal dose required to induce loss of the righting reflex in 50 per cent. of the animals and the duration of action the interval between the loss and return of the reflex. This compound acted rapidly and was readily absorbed from the gastro-intestinal tract. Its duration of action was intermediate between the moderate- and long-acting barbiturates, but its actions on the higher centres differed qualitatively from the barbiturates. Small doses prolonged the period of sleep induced by hexobarbitone. Acute toxicity tests in mice showed it to be one-third to one-quarter as toxic as the barbiturates. Chronic toxicity tests in rats showed no pathological changes in the blood picture over a period of 8 weeks. Anticonvulsant tests showed this compound to antagonise convulsions induced by pentylenetetrazole. In dogs anæsthetised with pentobarbitone intravenous doses as high as 40 mg./kg. did not alter the systolic blood pressure or the rate and amplitude of respiration. Only pentylenetetrazole was a satisfactory antidote. G. F. S.

**Vasopressin, Assay of.** J. Dekanski. (*Brit. J. Pharmacol.*, 1952, **7**, 567.) The assay for vasopressin of the British Pharmacopœia, using the blood pressure response of the spinal cat, is far from satisfactory and the rat preparation of Landgrebe, Macauley and Waring is to be preferred. Its specificity has been increased by abolishing the usual pressor effects of adrenaline, noradrenaline and other compounds with dibenamine. A 4-point assay procedure is described, doses being repeated at 6 to 10 minutes interval. The accuracy was extremely high, a mean value for $\lambda$ from 30 assays being 0·042 with a standard error of $\pm$ 0·023. The responses are not affected by the presence of the pituitary oxytocic factor or small amounts of histamine. G. F. S.

***Veratrum viride* Extracts in the Treatment of Hypertension.** L. C. Mills and J. H. Moyer. (*Arch. intern. Med.*, 1952, **90**, 587.) This is a clinical study of the value of two commercial preparations (vergitryl and veriloid) containing the active alkaloids of *Veratrum viride* in the treatment of hypertension. The results obtained in the treatment of 61 patients indicates that veratrum preparations have a definite hypotensive effect on some patients, but that in a large percentage this effect is minimal and it is unlikely that the blood pressure will be reduced to normal levels. In addition, there is a high incidence of associated toxic reactions (nausea, vomiting, epigastric burning, weakness, faintness and increased salivation) which seriously limit the use of these preparations. For the treatment of hypertensive crises and encephalopathy, however, on a short-term basis, the administration of veriloid by continuous intravenous infusion is very effective. Usually, a priming dose of 0·5 $\mu$g./kg. of body weight/minute was given intravenously until a satisfactory hypotensive response was obtained. This was followed by an infusion containing 3·6 mg./l. at a rate of 10 to 100 drops/minute (continued for 18 to 96 hours). After the intravenous infusion, administration of the drug was continued orally or intramuscularly. From a comparison of the veratrum preparations with some of the newer ganglionic and adrenergic blocking agents the authors conclude that hexamethonium is the best single drug in the long-term oral treatment of hypertension, and that veriloid intravenously is the most satisfactory drug for short-term reduction of blood pressure in hypertensive crises. S. L. W.

**Vitamin $B_{12}$ and Isoniazid.** B. Rubin and J. C. Burke. (*Lancet*, 1952, **263**, 937.) The authors were unable to confirm a previous report that subcutaneous injection of cyanocobalamin (vitamin $B_{12}$) diminishes the acute toxicity of isoniazid in mice. Isoniazid (2 per cent. aqueous solution) and vitamin $B_{12}$ (0·002 or 0·032 per cent. aqueous solution) were injected subcutaneously into albino mice. No significant difference in LD50 was observed between mice receiving 0·30 ml. of the vitamin $B_{12}$ solution per 20 g. and those receiving an equal volume of saline solution instead of the vitamin. Among 50 compounds tested, only barbiturates and some related depressant agents appeared to offer useful protection. Dimercaprol produced only a transient suppressive action in high doses. G. B.

## BACTERIOLOGY AND CLINICAL TESTS

**Fluorescin Transfer from *Ps. pyocyanea* to Colonies of Other Bacteria.** L. Hurst and E. J. L. Lowbury. (*J. clin. Path.*, 1952, **5**, 359.) A plate of horse-blood agar containing 4 per cent. of Davis agar was inoculated with a streak of *Ps. pyocyanea* strain SP. Streaks of 11 different organisms were made perpendicularly to it, 6 organisms on each side with gaps of 2 mm. at the inner end of the streaks. After overnight incubation, the inner ends of streaks of 7 of the test organisms showed a green fluorescence under ultra-violet radiation, owing to absorption of fluorescin which had diffused from the *Ps. pyocyanea*. On continued incubation the fluorescence was masked by pyocyanin diffusing from the *Ps. pyocyanea*. The strongest acquired fluorescence was observed in coliform bacilli. In mixed cultures, fluorescent colonies of *B. coli* were observed, but fluorescence disappeared on subculturing. It is concluded that the picking of fluorescent colonies is not a justifiable method for obtaining pure cultures of *Ps. pyocyanea*, although a green or yellow fluorescence indicates the presence of the pseudomonas growing in a mixed culture. G. B.

**Isoniazid, *in vitro* Action of, on *Mycobacterium tuberculosis*.** R. Knox, M. B. King and R. C. Woodroffe. (*Lancet*, 1952, **263**, 854.) The growth-inhibiting concentration of isoniazid was determined against a number of micro-organisms in Dubos medium at 37° C. Isoniazid was found to have a highly potent and specific action on mycobacteria, especially *Myco. tuberculosis*. The inhibiting concentration had to be read after a standard time of incubation, such as 14 days, when the inhibiting concentration for *Myco. tuberculosis* H37Rv is as little as 0·01 μg./ml. On continued incubation, the end-point shifted, and the organism was found to grow in a concentration of 1·6 μg./ml. after 34 days' incubation. This was partly due to inactivation of the drug which occurs in uninoculated Dubos medium at 37° C., and partly to the emergence of resistant organisms. Increasing the temperature of incubation to 40° C. or adding streptomycin delayed the shift of end-point, although neither of these prevented inactivation of the drug by the medium. It appeared that increasing the temperature to 40° C. or adding streptomycin or *p*-aminosalicylic acid converted the bacteriostatic action of isoniazid into a more nearly bactericidal one. This is in agreement with the observation that toxic pyrexial patients with tubercular infections respond most dramatically to isoniazid treatment. Strains of *Myco. tuberculosis* resistant to 62·5 to 125 μg./ml. of isoniazid were readily isolated *in vitro*, and resistance appeared to be permanent. Isoniazid-resistant strains retained their resistance to streptomycin and *vice versa*. G. B.