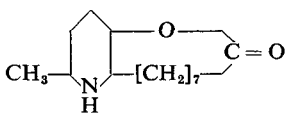
ABSTRACTS OF PAPERS PUBLISHED IN OTHER JOURNALS

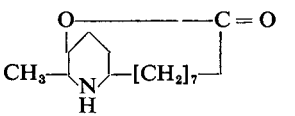
CHEMISTRY

ALKALOIDS

Carpaine, Constitution of. T. R. Govindachari and N. S. Narasimhan. (*J. chem. Soc.*, 1953, 2635.) Evidence is presented to show that carpaine, an alkaloid from *Carica papaya* L., is a derivative of piperidine instead of pyrrolidine (as assigned by Barger *et al.*, *J. chem. Soc.*, 1937, 711.) Dehydrogenation of ethyl-10-hydroxy-10:2′-pyrrolidinyldecanoate with palladium-charcoal yielded a pyrrole and not a pyridine derivative. Furthermore, ethyl carpamate, on similar dehydrogenation, yielded ethyl carpyrinate which was proved to be a 3- or 5-hydroxypyridine derivative. The formula I or II is suggested as the structure for carpaine.



(I)



(II)

A. H. B.

Ergotamine Phthalate. G. H. Svoboda and G. S. Shahovskoy. (*J. Amer. pharm. Ass., Sci. Ed.*, 1953, **42**, 729.) Central European ergots were powdered, defatted with benzene in the presence of aluminium sulphate, made alkaline with ammonia and the alkaloids extracted by percolation with benzene. An alkaloidal precipitate was obtained by the addition of skellysolve B, and dissolved in ether. When phthalic acid was added, ergotamine phthalate was precipitated but other ergot alkaloids remained in the solution. Ergotamine phthalate was obtained in the form of rhombic crystals by recrystallisation from acetone. Results of elementary analysis, physical constants, crystallographic and X-ray diffraction data and an infra-red absorption spectrum are given. G. B.

***Rauwolfia Serpentina* Benth, Alkaloids of; Reserpine.** M. W. Klohs, M. D. Draper, F. Keller, F. J. Petracek. (*J. Amer. chem. Soc.*, 1953, **75**, 4867.) Reserpine was obtained by chromatographing the "oleoresin fraction" from *Rauwolfia serpentina* on a silica acid-celite column. The alkaloid crystallised from methanol as flat colourless needles, m.pt. 252° C. (decomp.), $[\alpha]_D^{24° C.}$, − 122° (*c* 1·0 in chloroform) and the analytical data indicated an empirical formula of $C_{35}H_{44}O_{10}N_2$. Hydrolysis of reserpine with 0·75 N methanolic sodium hydroxide yielded reserpinolic acid, m.pt. 240° C., $[\alpha]_D^{24° C.}$, − 70 ± 3° (*c* 0·97 in water) and the analytical data indicated an empircal formula of $C_{24}H_{32}O_6N_2$. 3:4:5-Trimethoxybenzoic acid was also obtained as a hydrolysis product. Reserpine is therefore a diester containing a carbomethoxy group and a hydroxyl group esterified with 3:4:5-trimethoxybenzoic acid. There is also evidence of a tertiary nitrogen atom and an indifferent secondary nitrogen atom in the molecule analogous to the indole alkaloids previously shown to be present in this species. A. H. B.

Sempervirine, Isolation from *Gelsemium elegans* Benth. M. M. Janot, R. Goutarel and M. C. Perezamador y Barron. (*Ann. pharm. franç.*, 1953, **11**, 602.) Entire plants of *Gelsemium elegans* were separated into leaves, roots and stems, and small branches. Leaves were percolated with 96 per cent. ethanol and the extract evaporated *in vacuo* and dissolved in 2 per cent. hydrochloric acid. After allowing to stand for 3 days and filtering, the filtrate was made alkaline (*p*H 8·5) with sodium carbonate and extracted with ether followed by chloroform. The aqueous liquid was made strongly alkaline with sodium hydroxide and further extracted with chloroform. The ethereal extract was evaporated, dissolved in benzene, placed on an aluminium oxide column and eluted with benzene, followed by ether and ether-methanol. Gelsemine was obtained from the ether eluate, and sempervirine hydrochloride from the second chloroform extract by acidifying and recrystallising from methanol. Roots and stems were powdered, moistened with a 20 per cent. solution of sodium carbonate, dried and extracted with chloroform in a Soxhlet apparatus. The solution was concentrated, ether added and extracted with 2 per cent. formic acid, made alkaline and extraction continued as for the leaves. Koumine was obtained from the ether eluate and sempervirine hydrochloride from the second chloroform fraction. Sempervirine hydrochloride was prepared in the same way from the branches. G. B.

ANALYTICAL

Ascorbic Acid, Colorimetric Determination of. M. Schmall, C. W. Pifer and E. G. Wollish. (*Analyt. Chem.*, 1953, **25**, 1486.) A new assay method is given based on the reaction of ascorbic acid with diazotised 4-methoxy-2-nitroaniline in acid solution, followed by the development of a blue colour on making alkaline. The blue colour had an absorption peak at 570 mμ, the intensity reaching a maximum within one minute, although some fading occurred after 10 minutes. For concentrations between 0·5 and 2·0 mg./100 ml. of final solution a straight line calibration graph was obtained. The sensitivity of the reaction permits the determination of 0·5 mg. of ascorbic acid (10 μg./ml.). The method is specific for ascorbic acid in the presence of dehydroascorbic acid and all other vitamins normally found in pharmaceutical preparations; it can also be applied to various fruit juices and processed foods. R. E. S.

Caffeine in Tablet Mixtures, Colorimetric Determination of. R. A. Daoust. (*J. Amer. pharm. Ass., Sci. Ed.*, 1953, **42**, 744.) The following method may be employed for the analysis of tablets of aspirin, phenacetin and caffeine. It is simpler and more rapid than the A.O.A.C. method, but is not specific for caffeine. Dissolve with the aid of heat, a quantity of the powdered tablets equivalent to about 30 mg. of caffeine in 100 ml. of water. Place the solution on a water bath and add 10 ml. of a mixture of equal volumes of hydrochloric acid and water, and, drop by drop, 2 ml. of a 20 per cent. w/v solution of phosphomolybdic acid, and continue heating for 15 to 20 minutes to complete precipitation of the caffeine phosphomolybdate. Filter through sintered glass, wash the precipitate with dilute hydrochloric acid and dissolve in sufficient acetone to produce 100 ml. Determine the light absorption at 440 mμ using a spectrophotometer or a photoelectric colorimeter with a blue filter and calculate the quantity of caffeine from a standard curve prepared with the aid of a sample of pure anhydrous caffeine. Recoveries ranging from 98·46 to 102·72 per cent. were achieved. A modification for the assay of samples

containing only 3 mg. of caffeine is suggested. The use of a large excess of phosphomolybdic acid should be avoided as it produces a greenish deposit which interferes with the colorimetric determination. Substances such as phenazone interfere, and should be separated from the caffeine chromatographically. G. B.

Dextran, Determination of, with Anthrone. T. A. Scott and E. H. Melvin. (*Analyt. Chem.*, 1953, **25**, 1656.) The reaction of carbohydrates with anthrone in sulphuric acid was used to determine the concentration of dextran in aqueous solutions; the heat evolved by mixing with a sulphuric acid solution of anthrone yielded the heat required for the development of a blue-green colour. Details of the method are given together with the results of an investigation into the effect of time, temperature and acid concentration on the assay. The blank determination was considered to be the most likely source of error and 19 different chemicals at different levels of concentration were examined. The precision of the method was estimated by calculating standard deviations from 97 sets of duplicate blank determinations and 345 sets of duplicate sample determinations; the standard deviation of the blanks (0·0024) was more than 80 per cent. of the standard deviation of the samples. It was considered that the blank variability was due to extraneous carbohydrates. R. E. S.

Digitalis Glycosides and Aglycones, Specific Reaction for. P. Mesnard and A. Lafargue. (*Bull. Soc. Pharm. Bordeaux*, 1953, **92**, 160.) The following test is proposed. Dissolve 4 mg. in 4 ml. of methanol and add 1 ml. of a 1 per cent. solution of *p*-dinitrobenzene or 2:5-dinitrobenzoic acid in methanol, 7 ml. of water and 3 ml. of a 40 per cent. aqueous solution of sodium hydroxide. Glycosides containing one double bond in the lactone ring (digitoxin, gitoxin, oleandrin, digoxin and ouabain) and their genins yield a red colour, which is more intense and develops more rapidly when 2:5-dinitrobenzoic acid is the reagent. No colour is given by glycosides, such as scillaren, containing 2 double bonds in the lactone ring, or by ketosteroids. The *m*-dinitrobenzene (Raymond) and 3:5-dinitrobenzoic acid (Kedde) reactions are more sensitive and do not require so strongly alkaline a medium, but the colour is less stable and ketosteroids give a positive reaction. G. B.

Digitoxin Tablets, Analysis of. D. Banes and J. Carol. (*J. Amer. pharm. Ass., Sci. Ed.*, 1953, **42**, 674.) Commercial tablets were powdered and a quantity equivalent to 5 mg. of digitoxin was heated on a water bath with 15 ml. of methanol, cooled and extracted by shaking with 150 ml. of acidified sodium sulphate solution and 50 ml. of chloroform. The chloroform solution was evaporated and the residue analysed by chromatography on a celite 545 column using chloroform-benzene (1 + 9) as mobile solvent and formamide-water (2 + 1) as the stationary phase. The fore-run was examined by the Keller-Kiliani and *m*-dinitrobenzene tests, a negative result in the former and positive in the latter indicating the presence of digitoxigenin. Later fractions of the eluate contained digitoxin, and a gitoxin-containing residue was extracted from the celite column and submitted to the Keller-Kiliani, *m*-dinitrobenzene and Windaus-Schwarte (ferric chloride and sulphuric acid) tests. Good separation of the components was achieved by this chromatographic procedure. Each component was estimated colorimetrically against pure samples of digitoxigenin, digitoxin and gitoxin. Results were compared with the biological assay of the U.S.P., and the trinitrophenol test. The separation of digitoxin from impurities

by shaking with immiscible solvents was rapid and effective, but did not separate the glycoside from other steroids and tablet excipients so effectively as chromatography. G. B.

Glycerol, Volumetric Determination of. J. W. B. Erskine, C. R. N. Strouts, G. Walley and W. Lazarus. (*Analyst*, 1953, **78**, 630.) A simple acidimetric method, based on the oxidation of glycerol at room temperatures by sodium metaperiodate to yield formaldehyde and formic acid, is presented. The formic acid, after removal of the excess of periodate with ethylene glycol, is titrated with 0·1N sodium hydroxide using phenol red as indicator. It is necessary to exclude carbon dioxide and the oxidation must be carried out in the dark to minimise side reactions between sodium metaperiodate, formaldehyde and formic acid. Details of the procedure are given together with the results of investigations into the effect of light, temperature and oxidation time on the determination. Polyhydric alcohols and sugars interfere, but these are not usually present in the glycerol-containing products of soap-making and fat-splitting; of the likely organic impurities in these products trimethylene glycol does not react and polyglycerols do not yield formic acid. Glycols with adjacent hydroxyl groups, like ethylene glycol, react but produce only formaldehyde. The method has been checked against distilled glycerin, soap-lye crude glycerin, soap lyes and soaps containing known added amounts of glycerol, and also on commercial crudes, soap lyes and soaps, by comparison with the acetin and dichromate methods. R. E. S.

BIOCHEMISTRY

GENERAL BIOCHEMISTRY

Adrenaline, Noradrenaline and Hydroxytyramine in Insects. E. Östlund. (*Nature, Lond.*, 1953, **172**, 1042.) Experiments were carried out to see if adrenaline, noradrenaline and hydroxytyramine occurred in insects. Extracts of the whole animals of the yellow meal worm, the bee and other insects were made and assayed biologically and chromatographically. In all cases the three amines were found to be present and always there was considerably more noradrenaline than adrenaline. M. M.

Oxytocin and Vasopressin, Electrophoretic Studies of. S. P. Taylor, Jr. and V. du Vigneaud. (*J. biol. Chem.*, 1953, **205**, 45.) Beef vasopressin differs in amino-acid content from oxytocin only in having arginine and phenylalanine in place of leucine and *iso*leucine. Earlier studies of electrophoretic analysis in free solution have shown the two proteins to have different rates of migration (*J. biol. Chem.*, 1938, **123**, 45). High potency preparations of beef vasopressin were examined by the authors by zone electrophoresis on supporting media of filter paper, starch, and glass beads. The protein behaved as a single component, possessing high pressor and antidiuretic activity and measurable oxytocic activity. This last was not due to contamination with oxytocin, but was an inherent property of the vasopressin complex. Beef vasopressin was shown to be an ampholyte with an isoelectric point at *p*H 10·9. Electrophoresis can also be used to obtain pure samples of vasopressin from crude material. One sample increased in potency 7-fold after a single treatment. G. P.

Streptomycin: a New Metabolic Intermediate. W. W. Umbreit. (*J. Bact.*, 1953, **66**, 74.) A seven-carbon phosphorylated compound, 2-phospho-4-hydroxy-4-carboxy-adipic acid, is shown to be a metabolic intermediate, as determined by the incorporation of radioactive phosphorus. In *Bacterium coli*

it is formed on the addition of pyruvate and oxalacetate or fumarate and its formation is markedly inhibited by streptomycin. It is not yet apparent what rôle the new compound plays in bacterial or animal metabolism—it might be the actual intermediate entering the terminal respiration system, comparable to citrate in the Krebs cycle, or it might be a "coenzyme" whose presence is necessary for other reactions to proceed. Some attempts have been made to isolate the compound in sufficient quantity to perform metabolic experiments. It can be isolated readily from rat liver, but the small quantity present precludes this source as a starting material. Dried horse liver and fresh beef liver also contain the compound, but fractions containing it are contaminated by a brown waxy material which interferes with metabolism. S. L. W.

BIOCHEMICAL ANALYSIS

Adrenal Cortex Extracts, Chemical Assay of. D. Banes. (*J. Amer. pharm. Ass., Sci. Ed.*, 1953, **42**, 669.) Adrenocortical steroids were separated by chromatography on celite 545 columns saturated with formamide/water, using benzene as the mobile solvent. 11-Dehydrocorticosterone and corticosterone appeared in the first 70 ml., 17-hydroxy-11-dehydrocorticosterone in the next fractions and 17-hydroxycorticosterone last. Corticosterone was separated from 11-dehydrocorticosterone on a second column using benzene/*iso*octane (3 : 2) as mobile solvent. Using 1-mg. samples of the pure substances, recoveries of about 93 per cent. were achieved. Adrenal cortex extracts, when submitted to chromatography gave fractions contaminated with other corticoids. The following assay procedure is recommended. Dissolve the residue obtained by extraction of commercial tablets, aqueous or oily solutions in 2 ml. of methanol by warming on a water-bath, and cool. Add 100 mg. of Girard's reagent T and 0·2 ml. of acetic acid and allow to stand for 2 hours, shaking occasionally. Mix with 10 ml. of M sodium acetate and extract with chloroform to remove matter which has not reacted with the reagent. To the aqueous solution add 5 ml. of 3N hydrochloric acid, allow to stand for 1 hour and extract the regenerated ketones with chloroform. Separate the adrenocortical steroids by chromatography and estimate the quantity of 11-dehydrocorticosterone colorimetrically with tetrazolium chloride, corticosterone with sulphuric-acetic acid and 17-hydroxy-11-dehydrocorticosterone by the phenylhydrazine colour test. Calculated potencies are in agreement with the results of biological assay by deposition of liver glycogen in adrenalectomised animals. G. B.

Adrenaline and Noradrenaline, Quantitative Estimation of. W. W. Manger, E. J. Baldes, E. V. Flock, J. L. Bollman, J. Berkson and M. Jacobs. (*Proc. Mayo Clin.*, 1953, **28**, 526.) A modification is described of the method of Weil-Malherbe and Bone for the fluorimetric estimation of adrenaline and noradrenaline in blood plasma (*Lancet*, 1953, **1**, 974). The Weil-Malherbe and Bone method consists of adsorption of the amines on alumina, elution with acetic acid and condensation with ethylenediamine, giving fluorescent products. The two condensation products have different fluorescence spectra, which enables their estimation separately from two linear equations relating fluorimeter readings to concentration of the amine. The modification consists of the addition of sodium thiosulphate to the amine mixture before condensation with ethylenediamine. The thiosulphate depresses formation of the noradrenaline condensation product to about 22 per cent. of its original value, while leaving the adrenaline condensation product almost unaffected. Proportionality constants "b" for the linear equations were (i) adrenaline, with or without

sodium thiosulphate, $b_a = 2{\cdot}24$; (ii) noradrenaline, without sodium thiosulphate, $b_n = 0{\cdot}708$; (iii) noradrenaline, with sodium thiosulphate, $b'_n = 0{\cdot}153$. Aqueous solutions of adrenaline and noradrenaline and aqueous mixtures of the two gave mean recovery of adrenaline of 107 per cent. and noradrenaline 97 per cent. G. P.

Aureomycin, Carbomycin, Erythromycin, and Terramycin, Determination of, D. Perlman. (*Science*, 1953, **118**, 628.) Acid hydrolysis of aureomycin. carbomycin, erythromycin, and terramycin produced substances which reacted with arsenomolybdate reagent to produce blue coloured complexes. 10 to 40 μg. of antibiotic was evaporated to dryness in air, and 2 ml. of 6N sulphuric acid added followed by arsenomolybdate reagent; after heating for 15 minutes in a boiling water bath and cooling, the colour was measured at 660 mμ. The sensitivity of the method varied with the antibiotic under consideration; the range for terramycin and aureomycin was 2 to 40 μg./tube, for erythromycin 5 to 80 μg./tube, and for carbomycin 10 to 160 μg./tube. Terramycin alone reduced the arsenomolybdate reagent without hydrolysis. The method could not be applied directly to solutions containing carbohydrates and other substances which react when heated with the arsenomolybdate reagent. The antibiotics could be separated from carbohydrates by extraction from aqueous solution at *p*H 7·2 with an equal volume of chloroform, amyl acetate, *n*-butanol or methyl*iso*butyl ketone. R. E. S.

Dihydrostreptomycin, Colorimetric Determination of. G. C. Ashton, M. C. Foster and M. Fatherley. (*Analyst*, 1953, **78**, 581.) A colorimetric method, based on the reaction between guanido-materials, diacetyl, alkali, and α-naphthol is presented. Liquid samples (100 to 400 units of dihydrostreptomycin per ml.) are treated with diacetyl solution, potassium hydroxide solution and 1 ml. of α-naphthol solution, in that order; after 40 minutes the optical density is determined at 525 mμ and a graph is prepared from suitable dilutions of a standard dihydrostreptomycin solution. A standard graph should be prepared for each determination to allow for variations in room temperature and in reagents. The method described is applicable to streptomycin giving results similar to those by the ferric maltol method, but it cannot be used for streptomycin in fermentation broths as it gives the total guanidine-reacting material. Penicillin and its compounds do not interfere with the reaction; the standard error of the method is $\pm 1{\cdot}3$ per cent. R. E. S.

Penicillin G in Penicillin O, Determination of. J. L. Johnson, W. A. Struck, E. J. Scott and J. E. Stafford. (*Analyt. Chem.*, 1953, **25**, 1490.) A method is given for the determination of small amounts (less than 1 per cent.) of benzylpenicillin in allylmercaptomethylpenicillin (penicillin O), in which benzylpenicillin is oxidised with alkaline permanganate to benzoic acid by a modification of the method of Philpotts, Thain and Twigg (*Nature, Lond.*, 1947, **159**, 839). To avoid interference from oxidation products of penicillin O the resulting benzoic acid is extracted from ultra-violet absorbing materials and determined by means of its absorption maximum at 224 mμ, determinations at this wavelength being 15 times more sensitive than using the maxima in the 270 mμ to 280 mμ region. Experiments with known added increments of penicillin G showed a recovery of 86 ± 4 per cent.; the method is directly applicable to potassium penicillin O and to the procaine or 2-chloroprocaine salt after preliminary extraction of the organic base. R. E. S.

Tetrazolium Estimation of Urinary Steroids. J. Wheeler, B. S. Smith Freeman and C. Chen. (*J. lab. clin. Med.*, 1953, **42**, 758.) A comparison of the various methods available for the estimation of reducing steroids was made on normal individuals and on patients with normal and abnormal corticoid excretion; details of colour development in the tetrazolium method are given. The formaldehydogenic procedure was considered to be more specific than the tetrazolium method for the side chain characteristics of steroids, slightly lower values being obtained on normal subjects and in various pathological states with the formaldehydogenic procedure; phosphomolybdate reagent was less specific than the other reducing substances employed. The copper reduction method although more tedious and time-consuming gave results which agreed with the tetrazolium procedure. Variations in corticoid excretion as shown by the different methods was similar both in normal and in disease states. The stability of the reagents and of the colour developed in the tetrazolium procedure make this method preferable to the other studied. R. E. S.

CHEMOTHERAPY

D-Galacturonic Acid *iso*Nicotinyl Hydrazone, Antitubercular Activity of. P. P. T. Sah and S. A. Peoples. (*J. Amer. pharm. Ass. Sci. Ed.*, 1953, **42**, 612.) D-Galacturonic acid *iso*nicotinyl hydrazone was prepared by adding a solution of 25 g. of D-galacturonic acid in 150 ml. of hot water to a hot solution of 16·7 g. of isoniazid in 170 ml. of methanol, shaking, warming on a water bath, allowing to stand for 24 hours at room temperature, filtering and washing the precipitate with cold water and methanol. The substance was purified by recrystallisation from boiling water after treatment with a small amount of decolourising charcoal. It was shown to have a high activity *in vitro* and *in vivo* against *Mycobacterium tuberculosis* H37Rv, and to be much less toxic than isoniazid, the LD50 by intraperitoneal injection of a solution containing sodium bicarbonate being about 1·8 g./kg. G. B.

Salicylamide Derivatives, Toxicity and Analgesic Activity of. E. L. Way, A. E. Takemori, G. E. Smith, H. H. Anderson and D. C. Brodie. (*J. Pharmacol.*, 1953, **108**, 450.) 81 congeners of salicylamide were tested in rats for toxicity and ability to elevate the pain-response threshold to pressure stimulus. Most of them appear to be central nervous system depressants and some possess marked hypnotic properties. The various derivatives studied differ from the parent compound in groups substituted in the benzene nucleus on the amide nitrogen, and/or on the phenolic oxygen. The toxicity and analgesic potency of salicylamide may be decreased or increased by such chemical modifications with generally paralleled effects, but the changes in each effect are not always equivalent. *N*-methylation, *N*-ethylation, or *NN*-diethylation usually caused an increase in toxicity which was not always accompanied by increased analgesic potency. *N*-β-hydroxyethylation and *NN*-dimethylation usually resulted in decreased toxicity and potency. Substitution into the benzene ring at position 3, 4 or 5 with phenyl, bromo, hydroxyl or methoxyl groups generally decreased toxicity and potency. Four compounds were selected for more extensive study. 2-alkyloxy benzamide (S2–347) was found to be about 3 times as potent as salicylamide, with a comparable activity (LD50/AD50) ratio. *NN*-dimethyl-3-phenyl-salicylamide (S2–426) was found less toxic and more active than salicylamide and with an activity ratio 4 times that of salicylamide. 3-Phenylsalicylamide (S2–7) and *N*-(β-hydroxyethyl)-3-phenylsalicylamide (S2–62) were found to have a low order of toxicity and activity ratios greater than that of salicylamide, and these are being clinically investigated. S. L. W.

PHARMACOLOGY AND THERAPEUTICS

Digitalis Assays, Accuracy of. A. Elmqvist and L. Goldberg. (*Svensk farm. Tidsskr.*, 1953, **11**, 205.) The accuracy of digitalis assays by the guinea-pig method has been studied in a series of 60 determinations using 491 animals. When using 8 animals for the determination and 8 for the standard preparation, the limits are 91 to 110 per cent. with a probability of 0·05, corresponding to a divergence of 9·0 per cent. between animals in a single group and an experimental error of 4·5 per cent. in the determination. In an extreme case, where the variation in a single group amounted to 14·8 per cent. ($P = 0·05$) the limits became 87 to 115 per cent. At $P = 0·01$ the limits are on the average 88 to 114 per cent., and in an extreme case 81 to 124 per cent. G. M.

Ethylenediamine Tetra-acetic Acid (Versene) for Removing Fission Products from the Skeleton. J. M. Vaughan and M. L. Tutt. (*Lancet*, 1953, **265**, 856.) Elimination of isotopes of strontium, yttrium and the rare earths from bone is extremely slow and the effect of the sodium and calcium salts of ethylene-diamine tetra-acetic acid in hastening elimination of the isotopes from the bones of rabbits was investigated. The compound is a chelating agent, readily forming soluble complexes with the rare earths. The animals were given a single intravenous injection of either ^{91}Y or ^{90}Sr–^{90}Y equilibrium mixture (25 μc/kg.), followed by intraperitoneal injections of calcium disodium versenate or trisodium versenate. The dose was 250 mg. of the calcium disodium salt and 120 mg. of the trisodium salt once or twice a day for young rabbits, and 500 to 750 mg. of the calcium disodium salt once or twice a day for older animals. Determinations of the isotopes were made in bone and in the urine; amounts retained in other body tissues and excreted in the fæces were negligible. Calcium disodium versenate increased the excretion of ^{91}Y and ^{90}Y especially in young rabbits, but had no effect on the excretion of ^{90}Sr. In both age groups the effect was greater when the versenate was given immediately after the injection of yttrium. There is a marked reduction of ^{91}Y in the metaphyseal trabeculæ of young rabbits, suggesting that removal is more readily effected from areas of high metabolic activity associated with a good blood supply. Administration twice daily had little more effect than once daily. The calcium disodium salt is non-toxic and may well be of therapeutic value in people who ingest certain bone-seeking isotopes. H. T. B.

Gallamine Triethiodide in Treatment of Tetanus. J. H. McIntyre. (*Brit. med. J.*, 1953, **2**, 866.) 2 cases of tetanus are reported in which the use of gallamine triethiodide did not prevent death. The patients were children aged 4 and 7 and the periods elapsing between injury and onset of symptoms were 4 and 6 days respectively. Despite treatment with gallamine triethiodide, antitoxin, sedatives and antibiotics death occurred in 3 days and 1 day respectively. In the first case a total of 180 mg. of gallamine triethiodide intramuscularly and 170 mg. intravenously, during the 3 days, with paraldehyde and intravenous ethanol in addition, did not prevent convulsions occurring 2 or 3 times an hour. Respiratory embarrassment occurred 7 times, oxygen was often required and mucus had to be removed by frequent suction. In the second case a total of 404 mg. of gallamine with 29·5 ml. of thiopentone was given during the 23 hours the child lived in hospital, but numerous mild and many severe spasms occurred. H. T. B.

Hexamethonium with Polyvinylpyrrolidone. E. A. Murphy and J. Eastwood. (*Lancet*, 1953, **265**, 804.) The duration of action of subcutaneous injections of a solution of hexamethonium bromide, 20 per cent. w/v, in polyvinylpyrrolidone with 0·5 per cent. of chlorbutol as preservative were studied in 5 patients with severe hypertension and a grade III or grade IV retinopathy. The patients were kept in hospital for 14 days before treatment; they were ambulant but not allowed unusual exercise and blood pressures were recorded daily. The injections were given once daily and blood pressures were recorded at 2-hour intervals until the tenth or twelfth hour. Minimal systolic and diastolic blood pressures were usually reached within 4 hours; in 1 patient they were reached at the eighth hour. Appreciable hypotensive effect was noted for from 6 to 12 hours. Considerable day to day variation in response occurred despite efforts to standardise all conditions. Duration of action does not appear to depend on dose. Evidence of cumulative effect was shown by 1 patient. Side effects were dizziness, postural hypotension, constipation, loss of appetite, intestinal distension and colic. Faintness and postural hypotension might be delayed in onset beyond the usual 2 hours and the unpredictability of the action of the solution decreased its value. H. T. B.

Hypothermia, Production of. J. W. Dundee, W. E. B. Scott and P. R. Mesham. (*Brit. med. J.*, 1953, **2**, 1244.) The decrease in oxygen consumption by the tissues during hypothermia has led to its use in anæsthesia of the poor-risk patient and in major surgery. The normal body response to hypothermia has been reduced by deep anæsthesia, the use of muscle relaxants and of a mixture of chlorpromazine, pethidine and promethazine. Efficacies of the three methods are here compared in the anæsthetized dog and the constituents of the mixture assessed individually. Unselected mongrel dogs were used and basal narcosis was induced by intraperitoneal pentobarbitone (30 mg./kg.). 45 minutes later the following adjuvant drugs were given, mixed with hyaluronidase, by deep intramuscular injection, with the exception of pentobarbitone, which was injected intraperitoneally: pentobarbitone (15 mg./kg.); *d*-tubocurarine chloride (3 mg./kg.); chlorpromazine (2 mg./kg.); pethidine (4 mg./kg.); promethazine (2 mg./kg.). Artificial respiration was necessary with the *d*-tubocurarine. 15 minutes after administration of the adjuvant drugs the animals were covered with ice bags. Cooling was continued for 90 minutes. Rectal temperatures and shivering, if present, were recorded every 5 minutes. Oxygen uptake was measured directly with a spirometer. Oxygen uptake, heart rate and respiratory rate decreased linearly with fall in rectal temperature, where shivering was absent, heart rate and oxygen uptake generally showing an increase when shivering occurred. Apnœa was apt to occur at about 25° C. Cardiac arrest occurred in 3 animals at 23° C., 23·5° C. and 26·5° C., respiration being unaided in each case. Lower temperatures (21° C. to 22° C.) were obtained in dogs where respiration was fully controlled with oxygen. There was little to choose between deep anæsthesia, curarization and the chlorpromazine–pethidine–promethazine mixture in the rate and extent of temperature drop and abolition of shivering. The average rate of fall in rectal temperature was approximately double that obtained with the basic dose of pentobarbitone alone and shivering was almost completely abolished. Chlorpromazine was shown to be by far the most active constituent of the chlorpromazine–pethidine–promethazine mixture in the production of hypothermia. Pethidine was moderately effective in reducing shivering, but had little effect in aiding temperature fall. Promethazine had little effect on either shivering or temperature fall. When hypothermia had been induced with

the aid of pethidine, shivering returned after intramuscular injection of nalorphine. This might be due to a reversal of the analgesic effect of pethidine on thermal sensation or to a reversal of its central effects. G. P.

Hypothermia with Autonomic Block in Man. J. W. Dundee, T. C. Gray, P. R. Mesham and W. E. B. Scott. (*Brit. med. J.*, 1953, **2**, 1237.) A combination of induced hypothermia and a mixture of chlorpromazine, pethidine and promethazine in surgical procedure for 26 cases is described. The technique was considered to give the best chance of survival in seriously ill patients. There was a danger of serious cardiac irregularities at temperatures lower than 28° C. Also, difference in oxygen consumption between a patient at 28° C. and one at 25° C. was insufficient to warrant extra risks involved at the lower temperature. There was a prolongation of clotting time at the low temperatures obtained. Response to stretch of the myocardium at low temperatures is less efficient and a limit of 30° C. is suggested in cases with damaged myocardium. In one person cerebral circulation was cut off for 17 minutes at 25° C., but the respiratory centre continued to function as evidenced by normal respiratory movements. G. P.

Isoniazid Combined with Streptomycin or Sodium Aminosalicylate in Treatment of Pulmonary Tuberculosis. Fifth Report M.R.C. Tuberculosis Chemotherapy Trials Committee. (*Brit. med. J.*, 1953, **2**, 1005.) All of the 391 patients included in the trial were given isoniazid 200 mg. daily, in 2 equal doses by mouth, supplemented by by the following treatments:—Group SH: streptomycin 1 g. daily in 1 intramuscular injection; group S2H: streptomycin 1 g., in 1 intramuscular injection, twice a week; group 20 PH: sodium aminosalicylate 20 g. daily, in 2 equal doses by mouth; and group 10 PH: sodium aminosalicylate 10 g. daily, in 2 equal doses by mouth. In each group the combined treatment was continued for 3 months. 2 deaths occurred, 1 in an SH patient from acute nephritis near the end of the 3rd month, and 1 in a 20 PH patient after 30 days. 3 of the 20 PH patients were removed from the trial because of intolerance to sodium aminosalicylate and 2 more because of reactions possibly due to the aminosalicylate. There was no evidence of serious toxicity from isoniazid. The main comparison in the report is between the SH and the 20 PH treatments. They were of comparable efficiency in improving the general clinical condition, in lowering the sedimentation rate, in resolving pyrexia and in suppressing tubercle bacilli in the sputum. SH patients gained more weight and a higher proportion showed substantial radiographic improvement, but the differences were not statistically significant. The use of sodium aminosalicylate in combination with isoniazid prevents the emergence of strains resistant to either of the compounds, 0/29 cultures from 89 patients being resistant to isoniazid and only 1/28 resistant to sodium aminosalicylate. Results of the 10 PH treatment seemed to be as good as those with 20 PH but a larger number of patients must be treated before conclusions can be drawn. Preliminary comparison of sensitivity tests on cultures from patients after 3 months on SH and S2H treatments shows that while the development of resistance to streptomycin does not occur with either treatment, the incidence of resistance to isoniazid is noticeably greater with S2H. Judged solely from the clinical and bacteriological results at 3 months, sodium aminosalicylate 20 g. daily plus isoniazid 200 mg. daily is a highly effective combination of drugs ranking with the most efficacious treatments so far studied, namely streptomycin 1 g. daily plus isoniazid 200 mg. daily and streptomycin 1 g. daily plus sodium aminosalicylate 20 g. daily, and possessing an advantage over these treatments in that both drugs are administered by mouth. H. T. B.

Local Anæsthesia without Anæsthetic or Local Application. Study of the Mechanism of Action. R. Charonnat and P. Lechat. (*Ann. pharm. franç.*, 1953, **11**, 489.) Subcutaneous injection of a number of substances such as physostigmine salicylate, neostigmine and morphine induces anæsthesia of the rabbit cornea. Contrary to a previous report, no local anæsthesia is observed after the subcutaneous injection of pilocarpine nitrate. The local anæsthetic effect appears up to 45 minutes after the injection is made. The mechanism involved cannot be a blocking of cholinesterases, since the powerful anticholinesterase di*iso*propylphosphorofluoridate (DFP) does not produce any local anæsthetic effect on subcutaneous injection, whereas oxycodone (dihydrohydroxycodeinone), injected in a quantity of 10 mg./kg., produces an intense and lasting corneal anæsthesia, although it is at most a feeble inhibitor of cholinesterase. The effect of subcutaneous physostigmine salicylate is greatly reduced by atropinisation of the animal while that of procaine applied to the eye, is not affected. Sensitisation to acetylcholine may therefore be the explanation of the action of physostigmine, but it does not account for the effect of morphine and chlorpromazine. G. B.

Myasthenia Gravis—Course and Management of. D. Grob. (*J. Amer. med. Ass.*, 1953, **153**, 529.) 202 patients with generalised myasthenia gravis have been studied for about 8 years (range 1 to 34 years). 61 per cent. of the patients were women. Onset of the disease was at a lower age in women (average age 28) than in men (average age 43 years). About 25 per cent. of the patients had nearly complete remission of the disease for at least six months, the average being 4·6 years and some, 17 years. Neostigmine bromide did not influence the incidence or duration of remissions. 32 per cent. of the patients with generalized myasthenia gravis died between 3 months and 24 years after the onset (average 6 years), 13 per cent. are in complete or nearly complete remission (average 8 years after onset), 25 per cent. have improved to a moderate degree, 20 per cent. are unchanged and 10 per cent. are worse. The course of 44 patients who had their thymus glands removed and of 40 patients who had irradiation of the thymus was, in general, only slightly better than the course of 188 patients who had neither. Of 15 patients with a thymoma, ten died regardless of whether thymectomy was performed. When localised ocular myasthenia became generalised, it did so in 75 per cent. of the patients within the first year. Administration of potent anticholinesterase compounds, such as tetraethylpyrophosphate (TEPP) or octamethyl pyrophosphate (OMPA) resulted in more sustained muscular strength and endurance than with neostigmine, but the maximum strength attainable with any drug was the same. The most promising future investigations are the relation of myasthenia gravis to the glands of internal secretion and a study of the underlying defect in neuromuscular function. Exacerbation of the disease may occur before the onset of the menstrual period, after parturition or after the administration of thyroid hormone, adrenocorticotrophic hormones or of cortisone. G. F. S.

Neuromuscular Block in the Isolated Phrenic Nerve Diaphragm Preparation of Various Species. N. P. Bergh. (*Scand. J. clin. Lab. Invest.*, 1953, **5**, Suppl. 7.) Experiments are reported on the actions of decamethonium, suxamethonium (succinylcholine), *d*-tubocurarine and gallamine on the phrenic nerve-diaphragm preparation of the guinea-pig, puppy, kitten, young rabbit, golden hamster and the rat at room temperature (20° to 21° C.). In all preparations, except the rat, decamethonium caused a gradual reduction in amplitude of the single twitches and a tonic shortening of the muscle. The actions of suxamethonium

were about the same as decamethonium in the guinea-pig and hamster. The addition of tubocurarine to the bath before decamethonium or suxamethonium diminished or abolished the effect of these two drugs both in depressing the twitches and the tonic shortening. Tubocurarine and gallamine did not produce tonic shortening. Decamethonium and suxamethonium in the rat produced no tonic shortening of the muscle, only depression of the amplitude of the twitches. The reactions of the phrenic nerve-diaphragm preparation to different drugs vary from one species to another and the rat differs quantitatively and qualitatively from related rodents. G. F. S.

Noradenaline and Adrenaline in Blood and Urine, in Phæochromocytoma. U. S. von Euler, A. Lund, A. Olsson and P. H. Sandblom. (*Scand. J. clin. Lab., Invest.*, 1953, **5**, 122.) Phæochromocytoma in man is reported in which ordinary diagnostic methods and pharmacological tests failed to provide the diagnosis. Urine analysis showed a greatly increased amount of noradrenaline, while the level of adrenaline was only slightly above normal. The amount of noradrenaline in the urine was so large (over 1000 μg. per 24 hours), that it could be estimated directly on the blood pressure of the cat. The average concentration of the blood noradrenaline was 3·6 μg./100 ml. At operation a large tumour was found anteromedial to the hilus of the left kidney. Estimation of its adrenaline and noradrenaline content showed it to consist predominantly of noradrenaline. G. F. S.

Penicillin Reactions. R. A. Kern and N. A. Wimberley. (*Amer. J. med. Sci.*, 1953, **226**, 357.) Sensitivity to penicillin has increased to an extent that it is now the commonest cause of fatal anaphylactic shock. The antihistamine drugs control minor reactions but are useless against the severer reactions to penicillin. These occur in a multiplicity of forms including dermatitis, urticaria and anaphyllaxis. Sensitisation follows a previous sensitising dose, few people react after a first dose, but many people to-day have had penicillin. The majority of fatal cases of anaphylactic shock occur in asthmatics. While any penicillin preparation or mode of administration can precipitate a reaction, it is least after oral administration and most frequent after a depot preparation such as procaine penicillin. Sensitivity to local application is common. In most cases of penicillin sensitivity the antibodies are purely cellular and demonstrable by a patch test. In the severest types of sensitivity, circulating antibodies are usually found and may be detected by intracutaneous wheal tests. The duration of sensitivity is not clear. Milder types may clear up spontaneously in a matter of months while more severe types may last a lifetime. Possible penicillin sensitivity should be recognized from the routine history of the patient for personal or familial allergy, whether or no the patient has received penicillin before. Development of sensitivity in a patient who has not received penicillin before is unlikely during a single course of treatment not greater than 4 days. Patients suspected of a penicillin sensitivity should be given a cutaneous (scratch) test and if negative an intracutaneous test. Sensitization to penicillin is best prevented by avoiding its irrational use in trifling infections. It should not be used in allergic individuals unless the disease is serious, and the depot route should be especially avoided in these patients. Preference should be for the oral route of administration and the local use of penicillin by troches, sprays, aerosols and ointments should be discouraged. It is best to give another antibiotic in a potentially or proven sensitive patient. The treatment of anaphylactic shock is most difficult, symptoms may occur within a minute or two and death in 10 to 15 minutes. Treatment includes adrenaline by intravenous drip, intravenous

diphenhydramine, oxygen and adrenocorticotrophine hormone by intravenous drip or cortisone by mouth. G. F. S.

Primidone, Anticonvulsant Properties of. L. S. Goodman, E. A. Swinyard, W. C. Brown, D. O. Schiffman, M. S. Grewal and E. L. Bliss. (*J. Pharmacol.*, 1953, **108**, 428.) The anticonvulsant properties of primidone were compared with those of phenobarbitone by a variety of electrical-shock and drug-shock seizure tests in mice, rats, cats and rabbits. In mice and rats it was found markedly less neurotoxic than phenobarbitone. In both species, however, primidone was shown to be much less potent than phenobarbitone, except by the maximal electrical-shock seizure test in which it was more potent. The higher margin of safety in rats and mice is a direct result of its lower neurotoxicity. Primidone is able to protect cats and rabbits against maximal seizures induced by supramaximal electrical shock and by intravenous drug-shock with leptazol. It is many times more toxic in cats and rabbits than in rats and mice. Nephrectomy in rats increases the anticonvulsant potency of primidone twofold; rats and mice exhibit crystalluria after its administration. The crystals in rat urine have been identified as phenylethylmalondiamide, but it is thought unlikely that this is the anti-epileptic substance to which primidone owes its action. Primidone, in doses not much larger than those normally used in epilepsy, was able to alter the pattern of therapeutic electrical shock seizure in only 3 of 9 psychiatric patients in whom it was used, and caused side reactions (nausea, vomiting, dizziness, drowsiness, sedation, ataxia, motor weakness, skin rash) in 7. S. L. W.

Thiopentone and Hexobarbitone; Effect of Nephrectomy on Duration of Sleep. R. K. Richards, J. D. Taylor and K. E. Kueter. (*J. Pharmacol.*, 1953, **108**, 461.) Bilateral nephrectomy does not change the duration of sleep after an immediate injection of thiopentone or hexobarbitone in rats or rabbits. If the injection is given 3 or more hours after nephrectomy the duration of the thiopentone effect becomes markedly prolonged in both species, while hexobarbitone shows only a moderate prolongation in rats and none in rabbits. The degree of the increased thiopentone effect has been shown in rats to be in linear relation to the time after nephrectomy and the increase of the plasma non-protein nitrogen level. Ligation of the ureters leads to similar but less marked effects on thiopentone sleep. If the non-protein nitrogen plasma level is raised acutely in freshly nephrectomised animals by the injection of an artificial solution an immediate increase of sensitivity to thiopentone appears in these, but not in normal, animals. Sodium chloride or dextrose in amounts equiosmotic to the solution produce a similar but less pronounced effect. The fall of the barbiturate plasma level during the "normal" sleep period is the same in control and nephrectomised animals, but from then on the drop is significantly slower in the operated animals. It would appear that the post-nephrectomy state is associated with a somewhat greater sensitivity to the drug and a slower metabolic degradation of it. S. L. W.

Thyronines, Acetic Acid Analogues of Iodinated, Physiological Activity of. R. Pitt-Rivers. (*Lancet*, 1953, **265**, 234.) In goitre-prevention assays in rats, tetraiodothyroacetic acid (3 : 5-diiodo-4-(3′ : 5′-diiodo-4′-hydroxyphenoxy) phenylacetic acid) and triiodothyroacetic acid (3 : 5-diiodo-4-(3′-iodo-4′-hydroxyphenoxy) phenylacetic acid) showed about one-tenth of the activity of L-triiodothyronine. Diiodothyroacetic acid (3 : 5-diiodo-4-(4′-hydroxyphenoxy)phenylacetic acid) was relatively inactive. In experiments

(ABSTRACTS *continued on p. 273*).

products containing it. Among other minor points that have been noted are the surprisingly large recommended size (25 g.) of preputial suppositories or "bull cones" (p. 595), the erroneous statement on p. 120 to the effect that soft soap is a necessary ingredient of the wash prescribed by the Warble Fly (Dressing of Cattle) Order, 1948, and the somewhat gratuitous remarks on the addition of vitamins to mineral supplements in the relevant general monograph on p. 566. Such trivial blemishes are almost inevitable in a work of this kind, and those concerned with the production of the "B.Vet.C." may be rightly proud of this landmark in modern veterinary literature. ALASTAIR N. WORDEN.

(ABSTRACTS *continued from p. 271*).

on oxygen consumption in intact rats, triiodothyroacetic acid was shown to have a considerable activity in increasing the metabolic rate. It was not possible to calculate the relative potencies of triiodothyroacetic acid and L-triiodothyronine because of the high mortality rate at the higher dosage levels in the experiments. G. B.

Trifluoroethyl Vinyl Ether; Anæsthetic Action of. J. C. Krantz, C. J. Carr G. Lu and F. K. Bell. (*J. Pharmacol.*, 1953, **108**, 488.) Trifluoroethyl vinyl ether ($CF_3 \cdot CH_2—O—CH=CH_2$) is a volatile, colourless, mobile liquid, with an odour resembling that of vinyl ethyl ether. The boiling point is 42·7° C. and the specific gravity approximately 1·13 at 25° C. Its anæsthetic potency, when administered by inhalation to various species of animals, is approximately equal to that of ethyl ether. It produced no functional hepatic impairment in the dog, as shown by the bromsulphalein test, and produced no histopathological changes in the liver or kidneys of rats or dogs. Neither the monkey's nor the dog's heart showed any electro-cardiographic changes, and electroencephalograms in both animals were not dissimilar from those under anæsthesia with ethyl ether; the blood pressure of the dog was not significantly lowered. It does not appear to be decomposed readily by hydrolysis and the metabolic processes of the body do not appear to liberate fluoride. It presents less of a fire and explosion hazard than similar non-fluorinated ethers. It compares favourably with ethyl ether, ethyl vinyl ether and *iso*propyl vinyl ether as an inhalation anæsthetic in the dog, monkey and rat. The anæsthetic was administered by the open-drop method to a middle-aged woman during a rectal operation. Relaxation was good, and blood pressure and pulse essentially unaltered. Its cautious trial in man would appear to be warranted. S. L. W.

3:5:3′-Triiodothyronine, Biliary Excretion of the Glycuroconjugate of. J. Roche, R. Michel and J. Tata. (*C.R. Acad. Sci. Paris*, 1953, **255**, 1614.) A study has been made of the biliary excretion of 3:5:3′-triiodothyronine labelled with ^{131}I and followed by sodium sulphate labelled with ^{35}S. About 30 per cent. of the ^{131}I was excreted in 24 hours while only 3·4 per cent. of the ^{35}S was excreted, entirely in the first 8 hours. Chromatographic analysis indicated the excretion of 3 iodine products, one of which was 3:4:3′-triiodothyronine. The other two compounds were unknown but one of them was regenerated to 3:5:3′-triiodothyronine by β-glycuronidase and was probably a glycuroconjugate. The metabolism of thyroxine and 3:5:3′-triiodothyronine show much the same similarities. G. F. S.

(ABSTRACTS *continued on p. 280*).