ABSTRACTS OF PAPERS PUBLISHED IN OTHER JOURNALS

CHEMISTRY

ANALYTICAL

Aureomycin Hydrochloride, Spectrophotometric Assay for. L. J. Ravin and A. E. James. (*J. Amer. pharm. Ass., Sci. Ed.*, 1955, **44**, 215.) The method depends on the development of a bluish-green colour when phosphomolybdic acid and sodium hydroxide are added to solutions of aureomycin hydrochloride. The hydrogen ion concentration and quantity of phosphomolybdic acid required for the development of the maximum intensity of colour were determined experimentally, and the following assay method was evolved. Dissolve a sample containing about 25 mg. of aureomycin hydrochloride in 150 ml. of water, add 20 ml. of a 2 per cent. solution of phosphomolybdic acid, adjust the reaction to *p*H 5·5 to 6·5 by the addition of sodium hydroxide and add sufficient water to produce 1000 ml. Determine the light absorption at 405 mμ, the wavelength of maximum absorption. Calculate the quantity of aureomycin by reference to a standard curve based on the results of experiments with a sample of pure aureomycin hydrochloride. The method may be applied to tablets, capsules and surgical powder. Good agreement was obtained between this method and the assay based on the light absorption of aureomycin solutions at 440 mμ. G. B.

Creatinine in Alcoholic Solution, Spectrophotometric Determination of. L. Jacobbson and L. Paulsen. (*Scand. J. clin. Lab. Invest.*, 1955, **7**, 32.) Creatinine was dissolved in various solvents and the absorption in the ultra-violet region was recorded, using a Beckman spectrophotometer. The solvents used were distilled water, methanol, ethanol, propanol, butanol, heptane, pyridine and 0·1N hydrochloric acid. Creatinine dissolved in either 4 parts methanol or ethanol and 1 part water or in pure butanol showed absorption in the ultra-violet region with a distinct maximum at 235–236 mμ. Either no maximum or no absorption was obtained with the other solvents. The standard curve for creatinine in the ethanol-water solvent was a straight line passing through the origin and is thus in accordance with Lambert-Beer's law. Under identical conditions no maximum was obtained with creatine. M. M.

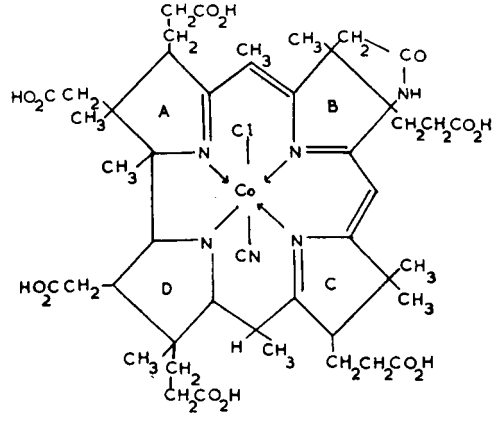
Erythromycin, Spectrophotometric Determination of. J. B. Tepe and C. V. St. John. (*Analyt. Chem.*, 1955, **27**, 744.) The characteristic ultra-violet absorption spectrum of hydrolysed erythromycin was found to offer the most promising method of analysis. Erythromycin itself showed a broad absorption band of weak intensity at 285 mμ; after hydrolysis by strong acid at elevated temperatures, maxima at 226, 267, and 485 mμ were produced, the absorption at 226 mμ having $E_{1\text{ cm.}}^{1\text{ per cent.}}$ approximately 150 and obeying Beer's law. Other degradation products of erythromycin absorb in the 226 mμ range and limit the usefulness of acid hydrolysis as an assay method, although a dilute acid-inactivated blank can be use to correct for the ultra-violet absorption of degradation products and impurities. After dilute alkaline hydrolysis, erythromycin exhibits strong absorption at 236 mμ, $E_{1\text{ cm.}}^{1\text{ per cent.}}$ 85. The procedure described was used for the determination of the potency of fermentation samples. Erythromycin was extracted from broth at *p*H 10 with amyl acetate or trichloroethylene, after which a procedure for nonaqueous samples was used. It was necessary to

restandardise the test on the basis of recoveries of erythromycin in the extraction procedure, which varied from 90 to 94 per cent. Good agreement was obtained between ultra-violet and microbiological assay methods. R. E. S.

Riboflavine, Determination of, by Light Absorption and Polarographic Methods. A. J. Zimmer and C. L. Huyck. (*J. Amer. pharm. Ass., Sci. Ed.*, 1955, **44**, 344.) The extinctions of solutions of riboflavine in 0·02N acetic acid were determined at 267, 270, 440 and 445 mμ. Beer's law was obeyed at concentrations from 2 to 7·5 μg./ml. Samples were assayed by comparison with a standard curve based on measurements of the extinctions at 270 and 440 mμ of solutions of riboflavine reference standard (2, 3 and 5 μg./ml.) in 0·02N acetic acid. It was established that the solutions are not affected by light under ordinary laboratory conditions, although prolonged exposure to the light of a "daylight" fluorescent lamp, caused decomposition of riboflavine, demonstrated by changes in the ratio of extinctions at 267 and 270 mμ, the latter being the more sensitive to the decomposition of riboflavine by light. Solutions of riboflavine in 0·02N acetic acid were polarographed from 0 to 1·5 volt, using a saturated calomel cell as reference. 0·1N potassium chloride was used as supporting electrolyte, and oxygen was removed by bubbling nitrogen through the solution. The diffusion current at 0·4 volt was measured and the residual current subtracted from this figure. The quantity of riboflavine in the sample was then read from a standard curve based on measurements in solutions of riboflavine reference standard containing 10 to 100 μg./ml. This method was suitable for tablets and some liquid preparations. Both methods were of good precision, but gave results slightly lower than the U.S. Pharmacopeia (fluorimetric) method. G. B.

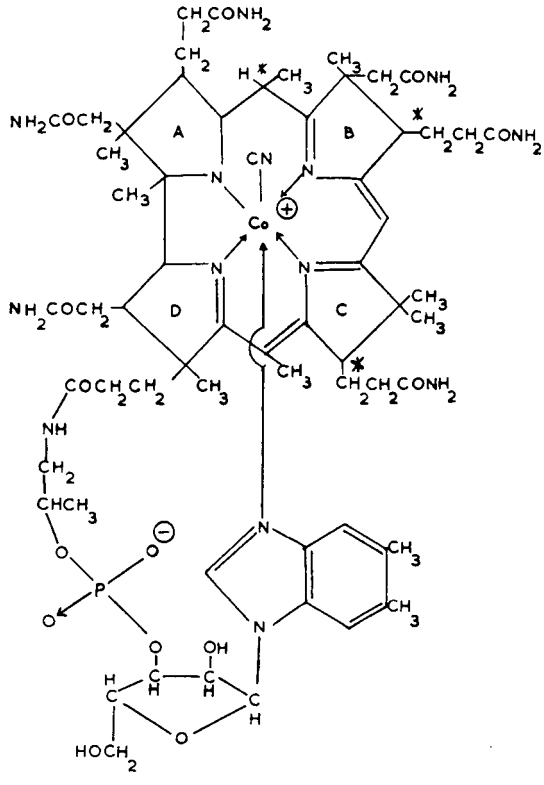
ORGANIC CHEMISTRY

Vitamin B_{12} and its Hexacarboxylic Acid Degradation Product, The Structure of. R. Bonnett, J. R. Cannon, A. W. Johnson, I. Sutherland, A. R. Todd and E. Lester Smith. (*Nature, Lond.*, 1955, **176**, 328.) Degradation of the crystalline nucleotide-free hexacarboxylic acid, from the alkaline hydrolysis of vitamin B_{12} previously described, has been carried out to fill in details of the molecular structure not revealed by X-ray crystallography. (*Nature, Lond.*, 1954, **174**, 1169.) A further communication (*Nature, Lond.*, 1955, **176**, 325) from Crowfoot Hodgkin, Pickworth, Robertson, Trueblood, Prosen and White published simultaneously with the present one describes the determination by X-ray crystallographic methods of the relative positions of all the atoms (excluding hydrogen) in the hexacarboxylic acid. These results taken with the chemical evidence have led to the structures proposed for the hexacarboxylic acid (I) and vitamin B_{12} (II). The formula of the hexacarboxylic acid has been revised to $C_{46}H_{60}O_{13}N_6CoCl,2H_2O$. The analytical figures are best accounted



(I)

for by the assumption that all eight single substituent atoms are present as carbon in methyl groups. Independent evidence for the existence of ring C has already been obtained by the isolation of 1 : 1-dimethyl-2-(2′-carboxyethyl) succinimide from chromic acid oxidation of a crude vitamin B_{12} hydrolysate, and the same substance has now been obtained by a similar oxidation of the pure hexacarboxylic acid. The five-membered ring attached to ring B of the hexacarboxylic acid, which X-ray examination reveals is not present in the vitamin itself, has been assigned a lactum structure on the basis of elementary analysis, infra-red data and the fact that the hexacarboxylic acid does not acquire an additional negative charge even at *p*H 11. An explanation is provided of the known conversion of B_{12} to a biologically-inactive crystalline substance when submitted to the limited action of alkali



(II)

in the presence of air, in terms of ring hydroxylation of the activated β-positions of the pyrrole rings, similar to that observed with chlorophyll derivatives. In support of this thesis it has been shown that acid hydrolysis of the oxidation product gives a mixture of penta- and hexa-carboxylic acid but no heptacarboxylic acid. Differences between Vitamin B_{12} and the porphorin series, as in the visible spectra and the failure of the former to yield maleimides on oxidation are explained by the fact that the rings A, B, C and D each contain at least one tetra-substituted β-carbon atom, so that the pyrrole rings are partly reduced. Vigorous hydrogen peroxide oxidation of the hexacarboxylic acid, however, does yield oxamide, the formation of which is in agreement with the placing of the conjugated double bond system in the molecule of the vitamin. The positioning of this system is confirmed by the action of *N*-chloroamides on vitamin B_{12}, when three moles of reagent are consumed in the formation of a stable product, a dichloro compound with a visible spectra displaced into the red. Chlorination is assumed to occur at the three positions marked*, followed by elimination of hydrochloric acid from the meso position between rings A and B to extend the conjugated system by formation of a sixth double bond. Biogenetic considerations support the proposed structure for vitamin B_{12}, for which a simple scheme of biogenesis can be formulated based on that already accepted for many natural porphorins. J. B. S.

GLYCOSIDES, FERMENTS AND CARBOHYDRATES

α-Peltatin Glucoside, The Isolation of, from the Rhizomes of *Podophyllum peltatum* L. A. Stoll, A. von Wartburg and J. Renz. (*J. Amer. chem. Soc.*, 1955, **77**, 1710.) A new glucoside was isolated from the more water-soluble fractions obtained by partition chromatography between different solvents during the isolation of the glucosides of podophyllotoxin and β-peltatin from the rhizomes of *P. peltatum*. It crystallises from acetone in colourless, long prisms m.pt. 168 to 171° C. (decomp.), $[\alpha]_D^{20}$ −128·9° (*c*, 0·5 in methanol), formula $C_{27}H_{30}O_{13}$. It is readily soluble in ethanol and fairly readily soluble in water, and gives a positive reaction with ferric chloride. This glucoside is easily hydrolysed by β-glucosidase at *p*H 5 into aglucone and glucose. The aglucone was found to be identical with α-peltatin. α-Peltatin glucoside exhibits antimitotic activity. A. H. B.

BIOCHEMISTRY

BIOCHEMICAL ANALYSIS

Bile Pigments in Serum, Chromatographic Determination of. B. H. Billing. (*J. clin. Path.*, 1955, **8**, 126.) Bile pigments ("bilirubin") in the serum of patients with obstructive jaundice consists of three related substances, bilirubin and pigments I and II. A quantitative method is described for their determination based on their separation by reverse phase partition chromatography. To 1 ml. of serum add 0·18 ml. of saturated ammonium sulphate solution and 2·5 ml. of ethanol. Stand in the dark for 30 minutes and remove the precipitate by centrifuging. A sample of the supernatant, containing 50 to 100 μg. of total bile pigments (previously determined by the method of Malloy and Evelyn), is evaporated to dryness *in vacuo* at room temperature. The dried supernatant is transferred quantitatively to the top of a kieselguhr chromatographic column, prepared in a special tube allowing easy separation of the bands, using not more than 0·5 ml. aqueous phase of a butanol-water system. The pigmented solution is run into the kieselguhr and when the top is almost dry 4·5 ml. of aqueous solution is added. The solution is allowed to flow through at a rate of not more than 1 ml. every 3 minutes until separation of the three pigments is achieved. The portions of the column containing the pigments are separated and each transferred to glass stoppered tubes. The pigments are converted to the corresponding azo-compound, extracted by shaking with 5 to 10 ml. of ethanolic diazotized sulphanilic acid and after centrifuging the kieselguhr residue is re-extracted with 5 ml. of ethanol. The solutions are combined for each pigment, the volumes measured and after 30 minutes read in a spectrophotometer at 525 mμ, from which the proportions of bilirubin, pigment I and pigment II are calculated. Methyl red is used as the standard. G. F. S.

Blood Serum, Determination of Total Lipides in. W. M. Sperry and F. G. Brand. (*J. biol. Chem.*, 1955, **213**, 69.) A method is described for the direct gravimetric determination of the unmodified total lipides of blood serum. For the extraction add 1 ml. of blood or plasma to 8·3 ml. of pure methanol in a 25 ml. volumetric flask, add an approximately equal volume of chloroform, bring just to the boil, cool, add chloroform to the mark, mix and filter. For purification two methods are described. In the first, pipette 20 ml. of extract into a vial 2 cm. in diameter and 8 cm. high, add water slowly until the vial is full and then lower into a 1 litre flask of water. Allow to diffuse for 18 hours,

removing the "fluff" which collects at the interface. In the second method, pipette 20 ml. of extract into a 25 ml. glass stoppered cylinder, add 4 ml. of water and shake vigorously for 1 minute. Allow to stand overnight to separate the two phases and wash the residue with 3 ml. of a chloroform-methanol-calcium chloride solution. The lipide extracts are then evaporated to dryness *in vacuo* or in an atmosphere of nitrogen, dissolved in chloroform-methanol, filtered into a 5 ml. volumetric flask and dried and weighed. The weight of lipides multiplied by 125 gives the concentration in mg. per 100 ml.

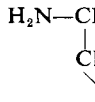
G. F. S.

Human Hæmoglobin, Estimation of. H. K. Prins and T. H. J. Huisman. (*Nature, Lond.*, 1955, **175**, 903.) Two methods have been developed for the separation and quantitative estimation of four different kinds of human hæmoglobin, namely, carboxyhæmoglobin-A (adult), B (sickle cell), C and F (fœtal). The best separation, using Amberlite IRC-50, was obtained at *p*H 6·50 (citrate buffer with a constant amount of citric acid and different sodium ion concentrations. Fœtal hæmoglobin was practically unabsorbed and separation of carboxyhæmoglobin-F was helped by a relatively low rate of flow of the effluent. A chromatogram is given of the four different hæmoglobins using a column of Amberlite IRC-50 (XE-64) of 13 cm. × 0·9 cm. at 10° C.; the yields were about 85 per cent. at 10° C., but could be improved by working at lower temperatures. The second method (cuvette method) employed a flat cuvette ("Lucite") of 3·0 cm. × 0·5 cm. × 20 cm. filled up to 15 cm. with resin; about 10–15 mg. carboxyhæmoglobin (in 1·0 ml.) was chromatographed using a sodium citrate-citric acid buffer (sodium ion concentration 0·15) of *p*H about 6 at 0° C. After the elution of 200 ml. effluent, siphoned into the cuvette at a rate of about 20 ml. per hr. a good separation of the four components was obtained. The mean rates of displacement were different for each component in the proportions of 1·33 (F): 1·00 (A): 0·72 (B): 0·34 (C). R. E. S.

CHEMOTHERAPY

Antirabies Vaccine for Human Use. F. B. Peck, Jr., H. M. Powell and C. G. Culbertson. (*J. Lab. clin. Med.*, 1955, **45**, 679.) A rabies vaccine prepared from embryonated duck eggs compared favourably with commercial vaccine from brain tissue, when tested in mice and monkeys. In dogs, a dose of 3 ml. of duck embryo vaccine produced the same percentage of antibody responses as a 5-ml. dose of commercial vaccine. During a clinical trial of duck embryo vaccine, antibody responses were demonstrated in 12 out of 13 subjects tested. The vaccine contained little if any of the brain antigen which is present in the rabbit brain vaccine, which may cause allergic encephalomyelitis. Duck embryo vaccine should not be given to persons sensitive to chicken egg albumin, on account of its antigenic similarity to duck egg albumin. G. B.

Cycloserine, Structure and Reactions of. P. H. Hidy, E. B. Hodge, V. V. Young, R. L. Harned, G. A. Brewer, W. F. Phillips, W. F. Runge, H. E. Stavely, A. Pohland, H. Boaz and H. R. Sullivan. (*J. Amer. chem. Soc.*, 1955, **77**, 2345.) Cycloserine is a new broad spectrum antibiotic elaborated by the soil organism *Streptomyces orchidaceus*. Isolation from culture filtrates was accomplished by absorption on anion exchange resins, elution with dilute mineral acid, and formation of a crystalline silver salt ($C_3H_5N_2O_2Ag$), from which the crystalline antibiotic was obtained as fine white needles from aqueous ethanol ($C_3H_6N_2O_2$), m.pt. 156° C. (decomp.) $[\alpha]_{5461}^{25}$ 137 ± 2° (*c*, 5 in



2N NaOH), $[\alpha]_D^{25}$ 112°, (*c*, 5 in 2N NaOH). Potentiometric titration (pKa′ 4·4 and 7·3) indicates that cycloserine exists in aqueous solution as a dipolar ion. These data, together with the infra-red spectrum, are consistent with structure I, D-4-amino-3-isoxazolidinone, for cycloserine. The reactions of cycloserine are recorded. A. H. B.

PHARMACY

NOTES AND FORMULÆ

Ascorbic Acid in Liquid Media, Stability of. F. J. Bandelin and J. V. Tuschhoff. (*J. Amer. pharm. Ass., Sci. Ed.*, 1955, **44**, 241.) Solutions containing ascorbic acid were assayed by the dichlorophenolindophenol method before and after storage at 25° C. and 40° C. for various periods up to 3 years. The effect of varying the *p*H and degree of aeration and of the presence of other substances was studied. The rate of decomposition was greatest in weak solutions, and increased with increasing *p*H value, being markedly accelerated above *p*H 4·0. Sucrose, sorbitol and propylene glycol had a stabilising effect, and ethanol, corn sugar and dextrose were less effective. Tragacanth, pectin, carboxymethylcellulose and methylcellulose, added to the solutions to increase their viscosity and thereby hinder oxygen exchange, appeared to accelerate the decomposition. The stability of ascorbic acid in syrup or sorbitol was increased by the presence of synthetic compounds of the vitamin B complex. G. B.

Carrageenin, Emulsifying Properties of. B. W. Fitzgerald and D. M. Skauen. (*J. Amer. pharm. Ass., Sci. Ed.*, 1955, **44**, 358.) Carrageenin (purified dry extract of Irish moss) was mixed with water in a mortar and allowed to stand for one hour to form a suitable mucilage. Oil was added in small quantities, triturating after each addition. The coarse emulsion formed by this process was improved by passing through a homogeniser or colloid mill. The best results were obtained with mucilages containing 0·2 to 0·4 per cent. of carrageenin. The emulsions were inferior to those prepared with acacia or, in the case of benzyl benzoate, with soap. Good results were obtained by using 0·4 per cent. of carrageenin to emulsify oil of turpentine. Since very low concentrations of carrageenin are required it is suggested that economies may be effected by using it in combination with other substances to reduce the total quantity of emulsifying agent required. G. B.

Dihydroxy Aluminium Sodium Carbonate, Preparation and Properties of. I. W. Grote, J. M. Holbert and M. Fox. (*J. Amer. pharm. Ass., Sci. Ed.*, 1955, **44**, 219.) Dihydroxyaluminium sodium carbonate was prepared by dissolving 42 g. of sodium bicarbonate in 350 ml. of warm water, and adding 102 g. of aluminium *iso*propylate, stirring vigorously. Stirring was continued until the precipitate became granular, when it was separated by filtration, washed to remove traces of sodium bicarbonate, and dried to constant weight. The substance was non-toxic when administered orally. When tested for antacid effect it rapidly neutralised the added acid and maintained the reaction above *p*H 3 for 2 hours under the conditions of test. The form of the neutralisation curve differed considerably from that given by a mixture of equimolecular quantities of sodium bicarbonate and dried aluminium hydroxide gel. G. B.

PHARMACOLOGY AND THERAPEUTICS

Aspirin and Ulcer. A. Muir and I. A. Cossar. (*Brit. med. J.*, 1955, **2**, 7.) The object of this investigation was to study the possible harmful effects of aspirin on the stomach, particularly in patients with peptic ulcer. As a result of fractional test meals and fæcal occult blood tests carried out on 20 patients suffering from peptic ulceration it was shown that aspirin tended to increase gastric acidity, and that evidence of gastric irritation, as shown by the presence of bloodstained mucus in the test-meal specimens, was commonly present. In order to study directly the effect of aspirin on the stomach 2 uncrushed 5-grain aspirin tablets were given with a little water to a series of patients 2 hours prior to gastrectomy for peptic ulceration. Three groups of 20 patients were given respectively tablets of an ordinary commercial brand of aspirin, tablets of a specially hard type, and tablets of soluble calcium aspirin. In the first group 12 patients showed evidence of mucosal irritation (3 severe); in the second group 8 showed typical acute erosive gastritis (moderately severe in 5); in the third group, receiving soluble aspirin only, 2 showed a very mild reaction, not regarded as abnormal. The specimens in this series showing the most severe acute erosive gastritis were all from patients with duodenal ulceration. Moreover, the erosions were obviously the result of the local irritant action of aspirin since they often took the shape of the aspirin granule, which remained *in situ*. Prior to the carrying out of clinical investigations 300 people were questioned about aspirin intolerance, without reference to their previous medical history. Approximately 1 in 20 confessed that aspirin gave them dyspepsia-heartburn, sometimes nausea, and occasionally epigastric discomfort. Of a series of 318 patients suffering from peptic ulcer who were questioned as to aspirin intolerance 110 were well aware that aspirin could only be taken at the risk of dyspepsia. Of 83 patients suffering with recurrence of ulcer pain 34 admitted to taking aspirin less than 24 hours before the recurrence of symptoms. Over a period of 7 years 15 patients with major dyspepsia were seen who were habitual aspirin takers and who were cured of their dyspepsia by its withdrawal. Of 166 cases of hæmatemesis, in 21 aspirin was clearly indicated as the major factor in precipitating the hæmorrhage. The authors conclude that aspirin should never be given to patients with peptic ulceration or to any who have gastric intolerance to it, however mild, and such an instruction should be given a prominent place in peptic ulcer advice charts. Calcium aspirin, especially the soluble form, does not have the same irritant action and can be used with impunity. S. L. W.

Bacterial Pyrogens on Splanchnic Metabolism and Cardiac Output, Effect of Subfebrile Doses of. L. W. Hamrick, Jr., and J. D. Myers. (*J. Lab. clin. Med.*, 1955, **45**, 568.) Erratic results are occasionally obtained in the study of splanchnic metabolism by the sulphobromophthalein extraction method, especially after intravenous injections of various materials, and since fever-producing doses of pyrogens increase hepatic blood flow and decrease removal of the dye by the liver an investigation was made to ascertain whether small doses of pyrogens, insufficient to produce fever, affected splanchnic metabolism. The pyrogenic material used was Pyromen, a purified polysaccharide from *Pseudomonas pyocyanea*, which was given intravenously in doses of 5 μg., and the study was carried out on 21 healthy hospital patients in the fasting state. Hepatic blood flow was determined by the sulphobromophthalein method, and the sulphobromophthalein clearance in ml./minute/sq. metre of body surface area was derived from the ratio of the clearance rate to the arterial

concentration. Splanchnic oxygen consumption was derived from the product of the hepatic blood flow and the average of two determinations of the arterial-hepatic venous oxygen difference. Cardiac output was determined by the dye-dilution technique using azovan blue. In 3 patients studied before, and 1½ hours after, pyrogen administration the sulphobromophthalein clearance decreased, but there was no other consistent alteration. In 11 patients observed 2 or more hours after pyrogen administration there were striking changes from the values obtained in 63 controls. The mean decrease in sulphobromophthalein clearance was 33 per cent., the mean elevation of hepatic blood flow was 47 per cent., and the mean increase in splanchnic oxygen consumption was 18 per cent. Splanchnic glucose production was unaffected. The elevation of hepatic blood flow was not accompanied by a proportionate increase in cardiac output. Contamination of parenterally injected materials with small amounts of bacterial pyrogens is therefore a possible cause of erratic alterations of splanchnic metabolism. H. T. B.

Barbiturate Intoxication, New Treatment of. A. Shulman, F. H. Shaw, N. M. Cass and H. M. Whyte. (*Brit. med. J.*, 1955, **1**, 1238.) The treatment suggested involves the use of two new barbiturate antagonists, β-methyl-β-ethylglutarimide (bemegride NP13) and 2:4-diamino-5-phenylthiazole hydrobromide or hydrochloride (amiphenazole D.A.P.T.). Bemegride is the more active antagonist but amiphenazole, although a weak antagonist, is a good synergist to bemegride and an excellent respiratory stimulant. High dosage of the substances, especially of bemegride, can cause convulsions in normal or barbiturized animals but virtually no signs of toxicity were observed in any of the authors' series of 41 cases. One death occurred but was not thought to be due to the treatment. The recommended treatment of barbiturate poisoning is as follows. If laryngeal and pharyngeal reflexes are absent, as ascertained by passing a laryngoscope, a cuffed tube is inserted and the stomach contents aspirated, but gastric lavage is not attempted. A clear airway and adequate oxygenation are ensured. Bemegride is given as a 0·5 per cent. solution in normal saline, and amiphenazole as a 1·5 per cent. solution in saline. A 5 per cent. dextrose intravenous drip is set up and every 3 to 5 minutes, by means of two 20 ml. syringes, there is injected into the rubber tubing of the apparatus 1 ml. amiphenazole solution and 10 ml. bemegride solution. If the response causes concern, dosage is halved. The injections are continued until the patient is brought to a "safe state," a state of light anæsthesia denoted by a return of tone and reflexes; in a deeply comatose patient this may take 2 hours. Total dosage of 200 ml. bemegride solution and 20 ml. amiphenazole solution is usually adequate. Once the safe state is attained, the endotracheal tube is removed and the patient treated as if recovering from light anæsthesia. Toxic effects are unlikely with the specified dosage. Vomiting and retching, perhaps with slight flickers of the fingers, are the earliest signs; if they occur treatment is suspended, and if they are severe a small intravenous dose of thiopentone sodium is given. If the patient's condition regresses after reaching the safe state, further treatment is necessary. The advantages of this procedure are that it minimizes the duration of endotracheal intubation, it minimizes the immediate and remoter risks to the patient's life and it avoids the need for prolonged strict nursing. H. T. B.

Bis-Quaternary Hypotensive Agents, Sites of Action of. C. J. Cavallito, A. P. Gray and T. B. O'Dell. (*Arch. int. Pharmacodyn.*, 1955, **101**, 38.) A study of a series of 1:3-bis-quaternary ammonium compounds of type $A^{+}(CH_2)_3B^{+}$ are described in which A is a β-carboline nucleus joined through

the pyrido-*N* and B is a small cationic group. Compounds in which B is smaller than triethylammonium are potent hypotensive agents with predominantly a central action accompanied by varying degrees of peripheral activity. The trimethylammonium compound has an intense hypotensive activity mediated through a probable central action and ganglionic blockade. The *N*-methyl pyrrolidinium derivative shows a greater central activity and less ganglionic blocking activity. The triethylammonium derivative shows little central and ganglionic activity but parasympathetic blocking activity is still present. The diethylmethyl derivative shows intermediate activity. The relationship of chemical structure to pharmacological activity is described. G. F. S.

Chlorpromazine in Acute Alcoholism. E. H. Mitchell. (*J. Amer. med. Sci.*, 1955, **229**, 363.) In the treatment of 400 cases of acute alcoholism equally divided into chlorpromazine-treated and barbiturate-treated groups the following procedures were carried out. On admission the patients in the chlorpromazine group were given 50 mg. intramuscularly or intravenously; after this they were given 50 to 100 mg. orally every 4 hours. The patients in the barbiturate group were given 250 mg. of quinalbarbitone intravenously and 60 mg. of butobarbitone and 1·5 g. of mephenesin every 3 hours until bedtime. In the chlorpromazine group effective sedation was achieved in 85 per cent. of the patients. Moreover, in this group, as compared with the barbiturate group, the nursing was simplified in that the patients were more amenable to suggestions, there were fewer falls from bed, the patients could retain food sooner, and they were ready to be discharged from the hospital on an average 24 hours earlier. There was no appreciable difference in the readmission rate for the two groups. In the patients receiving chlorpromazine mild postural hypotention was noted in 43 cases, and severe hypotention with syncope in 7 additional cases. There was one death in this series in a poor-risk cardiac patient with a cirrhotic liver who died suddenly following an attack of syncope 2 days after admission. Tachycaria was noted in 22; the heart rate returned to normal on discontinuance of chlorpromazine. S. L. W.

Chlorpromazine in Psychiatry. G. F. Vaughan, D. M. Leiberman and L. C. Cook. (*Lancet*, 1955, **268**, 1083.) The effects of chlorpromazine on 224 recent and chronic neurotic and psychotic patients were studied. The drug was given either by intramuscular injection, followed by oral administration of tablets, or by the oral route alone. With the former method, up to 150 mg. daily, usually in three doses, was injected for 4 days. Owing to the low *p*H the solution is irritant to the tissues, but if the drug is given by deep intramuscular injection there are few complaints of soreness, though indurated areas are produced in some and may persist. In 1 case out of 33 so treated a cold abscess formed. There would appear to be some evidence that the parenteral route may be more potent than the oral. Dosage by mouth was started at 75 or 150 mg. daily in 3 doses, and varied according to response up to 450 mg. daily. Chlorpromazine is not a curative drug but it effectively controls the symptoms of psychomotor over-activity, aggressiveness, agitation, and psychitic tension, and is particularly valuable in the treatment of chronic over-active deteriorated schizophrenics, mania, schizophrenic excitement, and patients who are unsuitable for electroconvulsion therapy or relapse after an initial improvement after it; it is not a substitute for this latter therapy or other forms of physical treatment where these are indicated. It is of considerable value in the large mental hospital ward; patients who are a continual source of disturbance may become quiet, co-operative, occupied and able to leave the hospital for short periods of

leave. Of the 224 patients in this series 22 per cent. developed sufficiently severe complications to stop treatment. Major symptoms occurring either alone or in combination were severe collapse (9), persistent pyrexia (8), persistent pains in legs or abdomen (7), persistent rashes (4), gross confusion (4), severe headaches (4), jaundice (3), vomiting (3), severe nausea (3), persistent tachycardia (3), constipation (3), convulsions (2), facial œdema (2), parotitis (2), severe cyanosis of the legs and trophic ulcers (2), marked depression (2), cardiac failure and œdema of the ankles (2), auricular fibrillation (1), diarrhœa (1), and hæmatemesis (1). The authors conclude that chlorpromazine is a valuable though limited addition to the therapeutic armamentarium of the psychiatrist. S. L. W.

Cortisone in Pyrogen-induced Fever, Antipyretic Action of. E. Atkins, F. Allison, Jr., M. R. Smith and W. B. Wood, Jr. (*J. exp. Med.*, 1955, **101**, 353.) The authors have investigated the 3 possible ways in which, on the basis of existing knowledge, cortisone may act in suppressing a febrile response to pyrogens. It may interfere with the leucopænia which precedes the onset of fever. It may alter the composition of the recipient's serum and thus modify the effect of the serum factor on which the action of pyrogen appears to depend. Thirdly, it may influence some later stage of the fever-producing sequence. The pyrogens used were Pyromen, a purified polysaccharide from a *Pseudomonas* species, and native dextran having an average molecular weight between 200,000 and 300,000, the dose (5 μg./kg. body weight of Pyromen and 200 mg. of dextran) being sufficient to give a 1° to 2° F. temperature rise in normal rabbits. Using 10 control rabbits, and 10 rabbits given 25 mg. of cortisone intramuscularly twice a day for 3 days preceding the experiment and a further 25 mg. on the morning of the experiment, it was found that the temperature response to Pyromen was effectively blocked whereas the fall in leucocyte count was not significant. With dextran the temperature response of 7 untreated rabbits was greater than the response to Pyromen but the response in the cortisone-treated rabbits was even more effectively blocked while the fall in the leucocyte count was the same in each group. It follows that the antipyretic effect of cortisone is not due to any effect on the reaction of leucocytes to the injected pyrogen. The serum factor shortens the time lag between injection of a pyrogen and the resulting rise in temperature; it is present in normal serum but not in the serum of animals rendered tolerant to pyrogens by a course of injections. In order to determine whether cortisone has any effect on the serum factor, experiments were carried out to determine whether there was a depression of the activity of serum factor in cortisone-treated rabbits and whether cortisone failed to suppress a response to pyrogen previously exposed to the active factor. In the first experiment, a pyrogen consisting of typhoid vaccine incubated with serum from cortisone-treated rabbits was injected into 7 rabbits rendered tolerant to the vaccine by daily injections. There was a marked shortening in the duration of the latent period but the shortening was the same as was obtained with a similar vaccine incubated with serum from normal rabbits, showing that cortisone does not significantly alter the serum factor activity. In the second experiment, cortisone-treated rabbits were challenged with typhoid vaccine incubated in normal serum, the results being compared with those obtained previously on the same animals using a suspension of typhoid bacilli in pyrogen-free saline. Cortisone was just as effective in suppressing the fever due to the incubated vaccine as that due to the saline suspension, showing that the antipyretic effect is not due to any action on the serum factor. It follows by exclusion that the antipyretic action of cortisone is exerted at some later stage of the fever-producing mechanism. H. T. B.

Deoxycorticosterone, Effect of, on the Reticulo-endothelial System. T. Nicol and R. S. Snell. (*Nature, Lond.*, 1955, **175**, 995.) Deoxycorticosterone acetate had little or no effect on the activity of the reticulo-endothelial macrophages in the spleen, liver and lymph-nodes of the guinea-pig. In this respect it differed from cortisone, which depressed phagocytic activity, especially in the spleen. The state of activity of the macrophages was measured by histological examination of their uptake of trypan blue, administered daily over a period of six days before the animals were killed. Treated animals received 2 or 5 mg. deoxycorticosterone daily by intramuscular injection for one to two weeks before being killed. G. P.

Dexamphetamine, Anticonvulsant Properties of. W. M. Alexander and L. C. Weaver. (*Arch. int. Pharmacodyn.*, 1955, **100**, 472.) Experiments in mice show that dexamphetamine itself has no anticonvulsant properties against electrical and chemical induced convulsions, and in conjunction with phenobarbitone did not alter the anticonvulsant potency of this barbiturate. It did reduce the toxicity of phenobarbitone, thus improving its safety index. G. F. S.

Dimercaprol, Hypoglycæmic Effect of. W. J. H. Butterfield. (*Lancet*, 1955, **268**, 489.) 15 severely burned patients were observed to develop hyperglycæmia and glycosuria about 5 days after their injury when force-fed to offset the expected loss of weight. Abnormal carbohydrate metabolism lasted for days, weeks, or months, the duration being shorter in children than adults. The abnormality seemed to be related at first to increased adrenocortical activity. The hyperglycæmia was shown to be insulin-resistant, the resistance being most pronounced within 3 weeks of injury, and less from 3 to 13 weeks after injury, the diabetes becoming insulin-sensitive if it lasted over 13 weeks. Since it has been suggested that the effects of increased adrenocortical activity in animals may be related to altered thiol (SH) metabolism, and since several SH enzyme systems take part in glycolysis, it was decided to study the effect of dimercaprol, an SH compound, on the glucose tolerance of burned patients. Dimercaprol, 250 mg. in oil intramuscularly, was given to 9 burned patients with hyperglycæmia at the start of a glucose tolerance or a glucose-insulin-tolerance test. The results showed that the dimercaprol injection slightly improved glucose tolerance in these patients when given alone in the early phase of greatest insulin resistance and when given with insulin from 3 to 13 weeks after injury. In these patients the blood keto-acid levels showed a smaller rise an hour after the start of tests involving dimercaprol than in corresponding tests without dimercaprol. Longer trials were then carried out with 7 diabetics whose daily insulin requirements varied from 24 to more than 320 units; in 2 cases the insulin requirements were sufficiently high to indicate insulin resistance. After control periods lasting from 2 to 5 days the patients were given intramuscular dimercaprol 5 per cent. in oil 4 ml. four times daily for 3 days and insulin. In all but 2 cases the glycosuria diminished on the 3rd day of treatment with dimercaprol and insulin; the same trends were observed in the blood sugar levels. Preliminary studies of blood-pyruvate levels showed high values an hour after insulin was given in the glucose-insulin-tolerance tests; these values were lower after dimercaprol treatment. In one of the 2 insulin-resistant cases on a diet excluding the supplementary glucose there was a daily urinary excretion of 11 g. of glucose on insulin 280 units a day; on the same amount of insulin, with 4 ml. of dimercaprol 5 per cent. in oil daily, the glucose excretion was 8 g.; and this was reduced to 2 g. when the insulin was given with 8 ml. of dimercaprol daily. It would seem therefore that dimercaprol given in conjunction with insulin may improve glucose tolerance in the circumstances of these investigations, especially in patients with possible insulin resistance. S. L. W.

Noradrenaline and Adrenaline in Urine, Excretion in Normal and Pathological Conditions. A. Pekkarinen and M-E. Pitkänen. (*Scand. J. clin. Lab. Invest.*, 1955, **7**, 8.) Using the fluorescence method described in *Scand. J. clin. Lab. Invest.*, 1955, **7**, 1 the mean daily excretion of adrenaline and noradrenaline (as noradrenaline equivalent) in the urine of normal, healthy adults was 81 μg. The individual results varied between 31 and 185 μg. The concentration in the urine varied between 3 and 17 μg. per cent. In 26 patients with hypertension and some other pathological conditions, one had a paraganglioma with a urinary excretion of 1354 μg. of noradrenaline per day. In two other patients there was an increased output but the other 23 showed a normal excretion. In patients receiving an infusion of noradrenaline in surgical shock, a small percentage of the amount of noradrenaline infused was found in the urine during the following 3 days. M. M.

Pentolinium Tartrate in the Long-term Treatment of Hypertension. A. Agrest and S. W. Hoobler. (*J. Amer. med. Ass.*, 1955, **157**, 999.) 31 patients with severe or complicated hypertensive disease were treated with orally administered pentolinium tartrate, with or without reserpine. Treatment was started by the administration of 20 mg. of pentolinium tartrate at 8 a.m., 3 p.m. and 10 p.m., the dose being increased by 20 mg. increments daily until a lowest systolic blood pressure of 110 to 130 mm. Hg with the patient standing was achieved consistently. It was later found possible to lower this minimal systolic blood pressure to 90 to 100 mm. Hg if the medicament was well tolerated. Constipation enhanced the effect of the drug and strict attention to bowel function early in the treatment was most important. The combined effects of a dose of pentolinium tartrate taken in the morning plus the noon meal produced a blood pressure "trough" at about 2 to 3 p.m. if the drug was taken immediately before breakfast and luncheon is eaten at 1 p.m. A 20 mg. increment in the dose was recommended if "trough" blood pressures had fallen almost to the desired level. Doses were increased by 20 mg. at 3-day intervals if results were unsatisfactory. Reserpine, 0·25 mg. 3 times daily, was also given in most cases. Hydrallazine was occasionally given in addition to pentolinium, but it rarely produced additive effects and its use was abandoned. A median reduction of 38 mg. Hg in the mean daytime standing blood pressure and of 23 mm. Hg in the mean recumbent blood pressure was estimated to have occurred in this series, and a notable improvement in the manifestations of congestive heart failure and of hypertensive retinopathy was observed; the effect on cerebrovascular manifestations was less certain but seemed beneficial. No marked relief of moderate uræmia or of angina pectoris was seen. There were no serious complications, and tolerance was slow to develop. S. L. W.

Rauwolfia in Hypertension. S. Locket. (*Brit. med. J.*, 1955, **1**, 809.) This is a report on a group of 39 severely hypertensive patients (38 of whom had essential hypertension) treated for a minimum period of 6 months and a maximum period of 20 months with oral preparations of rauwolfia. All the patients were ambulatory and all had a minimum diastolic pressure of never less than 130 mm. Hg. Each patient was used as his own control, the treatment being alternated between active drug and control tablets without his, or the clinician's, knowledge. In the first 10 months of the trial the active preparation used was total root extract, 1000 mg. daily; subsequently total active alkaloids were used, 8 mg. daily. 16 of the patients received, in addition, 8 to 10 mg. daily of veratrum viride extract during the entire observation. Little difference in hypotensive effect could be observed between the total root extract and the total active alkaloids.

Of the 39 patients, 16 showed no consistent fall in diastolic blood pressure, 7 a slight fall, 12 an appreciable fall, and 4 a fall to below 100 mm. Hg. Of the 16 patients with no consistent fall 4 had during the entire trial received either the control tablets alone or with veratrum viride. In the other 23 cases the fall in blood pressure occurred only while the patient was receiving the active rauwolfia preparation. Of the 34 patients receiving active rauwolfia tablets at some period during the trial 22 (67 per cent.) showed a fall in blood pressure of varying degree whilst taking the active preparation but not when on control. The combination of veratrum viride extract and rauwolfia gave 6 patients out of 13 who showed a hypotensive effect, as against 16 who showed a fall in blood pressure out of 21 receiving rauwolfia alone. The average age of patients who failed to respond to rauwolfia was 50 (range 34 to 64) whereas the average age of all patients who responded was 56 (44 to 64). There was evidence of a better response in males than in females. In every case in which the patient responded to the drug there was a delay in onset of the hypotensive effect, usually of 7 to 14 days, but sometimes as long as 4 weeks. In about half the patients several further weeks' treatment were necessary before the diastolic blood pressure reached its lowest level. Side-effects were seldom severe enough to necessitate cessation of treatment. Those complained of included diarrhœa, depression, fatigue, lack of energy, drowsiness, visual disturbances, fullness in the head, nasal congestion, nausea and vomiting. All patients with angina of effort found it necessary to continue to use nitroglycerin. The author concludes that rauwolfia is by far the most effective and useful orally administered hypotensive agent he has yet used, and is worthy of trial in every case of essential hypertension requiring treatment. S. L. W.

Tetracycline, Clinical Report on. R. L. McCorry and J. A. Weaver. (*Lancet*, 1955, **268**, 1102.) *In vitro* studies of antibacterial activity showed that tetracycline is effective against both Gram-positive and Gram-negative organisms, though the latter tend to have higher minimal inhibitory concentrations than do the former. Among the most sensitive organisms are certain strains of staphylococci, the pneumococci, the β-hæmolytic streptococci, some of the α-hæmolytic streptococci, and some enterococci. Among the resistant organisms are all strains of *Ps. pyocyanea* and some strains of *Staph. pyogenes*, *Strep. fæcalis* and *E. coli*. Most of the 87 patients in the series under review were treated for acute infections of the respiratory system. The best form of dosage was found to consist of an initial loading dose of 1 g. followed by 0·25 g. 6-hourly; this mode of treatment produced good blood levels. In pneumoccal lobar pneumonia the results obtained were good and in every respect equal to those following the use of chlortetracycline and oxytetracycline. On acute bronchopneumonia the results were variable and difficult to assess, but generally the results were again comparable with those of the two analogues. Of the 39 cases of pneumonia of all types it was considered that in 10 cases the response had been less than expected. In 17 cases of chronic bronchitis a good response was obtained in 13, the results being usually better than those following inhalational therapy with either streptomycin or penicillin. In 8 cases of bronchiectasis there was temporary improvement, with lessening of sputum in 6. The side-effects observed were mainly intestinal, flatulence, nausea and vomiting, diarrhœa, and pruritus ani. The authors conclude that tetracycline justifies further trial in that the incidence of side-effects appears to be less than that with the other substances of the tetracycline series and it seems to be quite as effective clinically. They consider, however, that penicillin should still remain the drug

(ABSTRACTS *continued on p. 968.*)