ABSTRACTS OF PAPERS PUBLISHED IN OTHER JOURNALS

CHEMISTRY

ALKALOIDS

Alkaloids of Two Brazilian Apocynaceæ. W. B. Mors, P. Zaltzman, J. J. Beereboom, S. C. Pakrashi and C. Djerassi. (*Chem. Ind.*, 1956, 173.) Reserpine was isolated in nearly 0·08 per cent. yield from the root bark of *Rauwolfia grandiflora* Mart. Chromatography of the "reserpine" fraction obtained from the whole plant of *Lochnera* (*Vinca*) *Rosea* (L.) Reichb., var. *Alba* (Sweet) Hubbd. yielded ajmalicine in 0·036 per cent. yield. Counter current distribution of the strongly basic fraction using 18 transfers and a chloroform-buffer (citrate-phosphate buffer of pH 7·4) system gave bright yellow crystals of serpentine in *ca.* 0·02 per cent. yield. Counter-current distribution (19 transfers) of the weak bases between chloroform and pH 6 buffer followed by crystallisation of fractions 7 to 15 from methanol furnished 0·009 per cent. of colourless crystals m.pt. 170–190° C. Repeated recrystallisation from methanol gave an analytical sample with the following constants: m.pt. 200–201° C. $[\alpha]_D^{21}$ + 50° (ethanol). (Found: C, 73·98; H, 7·70; N, 8·19; N–CH_3, 4·14; OCH_3, 9·00 which corresponds to $C_{20-21}H_{26-28}N_2O_2$ with one *N*-methyl and one *O*-methyl group. The alkaloid exhibited a typical indole ultra-violet absorption spectrum; it appears to be a new alkaloid and the name "lochnerine" is proposed. A. H. B.

ANALYTICAL

Antihistamine Combination, Spectrophotometric Assay of. S. M. Blaug and L. C. Zopf. (*Drug Standards*, 1955, **23**, 147.) A mixture of pyrrobutamine diphosphate and methapyrilene hydrochloride was assayed by preparing a solution in ethanol (95 per cent.) containing 0·002 per cent. of methapyrilene hydrochloride and 0·0012 per cent. of pyrrobutamine diphosphate. The optical density was measured at 225 mμ (maximum for pyrrobutamine diphosphate) and 241 mμ (maximum for methapyrilene hydrochloride) using a blank to compensate for the absorption due to the ethanol. The absorption spectra of the two compounds are very similar, but it was found possible to calculate the quantity of each substance present by the use of simultaneous equations containing additional terms to correct for the interference of one component at the absorption maximum of the other. G. B.

Belladonna Alkaloids, Colorimetric Assay for. W. Saski. (*Drug Standards*, 1955, **23**, 149.) The suggested method of assay depends upon the formation of a stable blue colour when a benzene solution of belladonna alkaloids is treated with oleic acid and cupric nitrate. The full intensity of the colour is developed within 24 hours at room temperature. Although the absorption is a maximum at 675 mμ, it is preferable to make measurements at 710 mμ so as to reduce the interference due to chlorophyll. Samples of belladonna herb are extracted, and volatile bases removed from the alkaloidal extractive as described in the U.S. Pharmacopeia XIV. The residue is dissolved in benzene and an aliquot quantity of the solution treated with oleic acid and cupric nitrate and allowed to stand for development of the colour. A further quantity of the benzene solution is treated with oleic acid and used as a control. The content

of alkaloids is calculated from the light absorption at 710 mμ by reference to a standard curve prepared by similar treatment of standard solutions of atropine in benzene. The results by this colorimetric method are in agreement with those of the U.S.P. XIV assay. G. B.

Heroin and Quinine, Spectrophotometric Determination of. M. J. Pro, W. P. Butler, and A. P. Mathers (*J. Assoc. off. agric. Chem., Wash.*, 1955, **38**, 849.) Absorption data for heroin, quinine, and mixtures of these alkaloids in 0·1N sodium hydroxide are given. Preliminary studies demonstrated that heroin was rapidly hydrolysed to morphine in 0·1N sodium hydroxide and that at 297·5 mμ, the point of maximum absorption of morphine, equal molar concentrations of quinine and morphine have almost the same absorption, while at 330 mμ, the quinine maximum, morphine does not absorb. Absorbance curves prepared in 0·1N hydrochloric acid show that the quinine absorbance is much greater than that of heroin at the quinine maximum, 250·5 mμ while at the 318 and 347·5 mμ maxima, even large concentrations of heroin do not absorb. At 285 mμ, the heroin maximum, equal weight concentrations of quinine absorb appreciably. From observed values at different wavelengths the two alkaloids can therefore be determined simultaneously in this acid medium. The separation of diluents insoluble in anhydrous methanol is advantageous because samples found in practice may contain many inert substances.

R. E. S.

Marcoumar, Colorimetric Determination of. J. Bednář. (*Československ. Farm.*, 1956, **5**, 26.) Marcoumar (3-(1′-phenylpropyl)-4-hydroxycoumarin) can be determined by allowing it to react with diazotised *p*-nitraniline, extracting the acidified reaction mixture with benzene and measuring the colour of the extract. One tablet, containing about 0·3 mg. of pure Marcoumar, is heated on a water bath for 10 minutes with about 12 ml. of 10 per cent. sodium acetate solution in a 25-ml. calibrated flask. After being cooled, the contents of the flask are made up to 25 ml. with 10 per cent. sodium acetate solution. The solution is filtered, and 2 ml. of freshly prepared diazotised *p*-nitraniline solution are added to 5 ml. of the filtrate; the mixture is set aside for 20 minutes at room temperature. It is then acidified with 1 ml. of concentrated hydrochloric acid and extracted with 10 ml. of benzene. The benzene solution is dried over sodium sulphate and its optical density is measured in a Pulfrich photometer with a S47 filter; a solution prepared without the sample is used as a blank. The amount of Marcoumar present is read from a calibration curve, constructed from readings obtained with known amounts (0·25 to 2·5 mg.) of pure Marcoumar. To prepare the diazotised *p*-nitraniline, 2 ml. of 1 per cent. *p*-nitraniline in N hydrochloric acid are mixed with 2 ml. of 5 per cent. sodium nitrite solution; after being set aside for two minutes at room temperature, the solution is treated with 2 ml. of 5 per cent. urea solution; after a further five minutes it is made up to 20 ml. E. H.

Nux Vomica, Colorimetric Assay of. M. Karmazin and L. Böswart. (*Pharm. Zentralh.*, 1956, **95**, 10.) 1·5 g. of coarsely powdered nux vomica is shaken vigorously with a mixture of 20 g. of ether and 10 g. of chloroform, then treated with 3 g. of 50 per cent. sodium carbonate solution. After shaking for 30 minutes, 3·5 g. of water is added and the mixture shaken again for 2 minutes. The layers are separated and the ether-chloroform solution is filtered through cotton wool: 20 g. of the filtrate is evaporated to dryness and the residue is rubbed down twice with 2 × 10 ml. of hot 1 per cent. sulphuric acid,

the liquid being filtered into a measuring flask. After cooling, the volume is made up to 25 ml. with the dilute acid. To 10 ml. of this solution in an ice bath is added 3 ml. of saturated solution of ammonium reineckate and the mixture is allowed to stand for 1 hour in the ice bath. The precipitate is filtered off on a 3G4 filter, washed with 0·2 per cent. ammonium reineckate solution, and freed from liquid by vacuum. After drying the filter tube with filter paper, the residue is dissolved in 2 ml. of acetone and washed with acetone until the runnings are colourless. The filtrate is made up to 10 ml. and the extinction is measured, using a green filter of 525 mμ. The method is standardised against a mixture of equal parts of strychnine and brucine. G. M.

Quaternary Ammonium Compounds, Determination of. R. Reiss. (*Arzneimit.-Forsch.*, 1956, **6**, 77.) The method is based on the extraction of the iodides of the quaternary compound with chloroform. About 10 ml. of a solution containing 1 to 2 mg. of the compound is treated with 1 ml. of 10 per cent. sulphuric acid and 2 ml. of freshly prepared 10 per cent. solution of potassium iodide, and extracted with 10 ml., then with 2 × 5 ml. of chloroform. The chloroform solution is filtered and made up to 25 ml. To 20 ml. of this solution is added 20 ml. of water, 1 ml. of sulphuric acid and 5 ml. of 1 per cent. solution of sodium nitrite. After shaking for 2 minutes, the chloroform layer is filtered into a 2 cm. cell and the colour is determined, using a S49 filter. The method is standardised against known weights of the compound. The method is not applicable in presence of certain alkaloids, or when the chloroform extract is itself coloured. In some cases extraction from an alkaline medium may remove the latter difficulty. The method has been tested with cetyltriethylammonium bromide, dodecylbenzyldimethylammonium bromide, di*cyclo*hexyldibenzylammonium bromide and di*cyclo*hexylcetylbenzylammonium bromide, but cannot be used with tetraethylammonium bromide. G. M.

Sulphafurazole, Colorimetric Determination of. J. Blažek and Z. Stejskal. (*Československ. Farm.*, 1956, **5**, 27.) Sulphafurazole (Gantrisin) is determined by titration with silver nitrate in the presence of sodium borate. For injections (containing 400 mg. per ml.), 50 ml. of 55 per cent. ethanol and 0·3 g. of sodium tetraborate are added to 1 ml. of solution in a 100-ml. calibrated flask; 40 ml. of 0·1N silver nitrate solution are added from a burette, the flask being thoroughly shaken during the addition. The solution is made up to 100 ml. and filtered through a dry folded filter, the first 20 ml. of filtrate being discarded. Concentrated nitric acid (3 ml.) and ferric ammonium sulphate solution (3 ml.) are added to a 25 ml. aliquot of the clear filtrate, and the excess of $AgNO_3$ is titrated against 0·1N ammonium thiocyanate. Tablets can be determined in the same way; a quantity of powdered tablets corresponding to 400 mg. of sulphafurazole is treated directly in a 100-ml. calibrated flask. The precision is ± 1·6 per cent. E. H.

Tetracycline Antibiotics, Separation of. P. P. Minieri and A. G. Mistretta. (*Science*, 1955, **122**, 1234.) The countercurrent distribution system of McIlvaine's phosphate-citrate buffer at pH 4·5 versus chloroform has been used for the analytical separation of mixtures of the known tetracycline antibiotics. In a 50-tube distribution with this system, the peak tubes observed were as follows: chlortetracycline 26, tetracycline 39, and oxytetracycline 44; these values corresponded to K aqueous/solvent values of 1·13, 3·90 and 8·80 respectively. After the theoretical curves for each component have been calculated, the percentage composition of a mixture such as one containing tetracycline and chlortetracycline can be calculated from the peak heights, determined

spectrophotometrically. Crude samples containing 300 to 500 μg./mg. gave satisfactory results in the identification of major components with 3 to 5 mg. placed in the first tube of a 50-tube apparatus containing 10 ml. of each phase. Pigments with strong absorption in the ultra-violet, such as anhydrotetracycline were usually found in the low-numbered tubes because of their solubility in chloroform; their presence did not, therefore, interfere with the ultra-violet determination of the peak tubes, which were carried out on the upper phase at a wavelength of 265 mμ after suitable dilution. R. E. S.

Vitamin K_3, Estimation of. V. Sathe, J. B. Dave and C. V. Ramakrishnan. (*Nature, Lond.*, 1956, **177**, 276.) A modification of the method of Reddy and Srinivasan (*Curr. Sci.*, 1948, **17**, 22) is described for the spectrophotometric estimation of micro quantities of Vitamin K. Vitamin K_3 solution (2 to 30 μg. 2-methyl-1:4-naphthoquinone) is shaken with 0·5 ml. of ethanol and 0·1 ml. of a saturated solution of 2:4-dinitrophenolhydrazine in 2 N hydrochloric acid. After 10 minutes 0·25 ml. of 20 per cent. sodium carbonate is added and shaken well until the green colour appears. Three ml. of amyl alcohol, 1 ml. of ethanol and 1 ml. of water are added, shaken and kept for 5 minutes. The amyl alcohol layer is taken and the density read at 635 mμ in a spectrophotometer. The colour is stable for 10 hours. G. F. S.

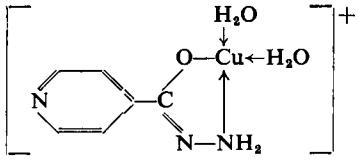
Water in Drugs, Determination of. G. J. Mulder and J. A. C. van Pinxteren. (*Pharm. Weekbl.*, 1956, **91**, 33.) A comparison of the Karl Fischer method with other methods for the determination of water in a number of pharmaceutical materials gave results in favour of the former. With the opium alkaloids, Karl Fischer results agreed generally with those obtained by drying at 70° C. *in vacuo*, but were in most cases appreciably higher than the loss on drying at 105° C. With dry extracts results were in all cases higher than those by ordinary drying methods; with thick extracts (belladonna, gentian, liquorice) higher results were generally obtained, but extract of valerian gave a much lower one since there was no interference by volatile products. For starches and pectin, results were in general slightly higher than those of ordinary drying. The method recommended for thick extracts is to rub the material (0·5 g.) down with sand (5 g.), take up with anhydrous methanol and make up to 25 ml.; an aliquot is then taken for the titration. G. M.

CHEMOTHERAPY

Isoniazid, Mode of Action of. A. Albert. (*Nature, Lond.*, 1956, **177**, 525.) Isoniazid has been shown to have an affinity for heavy metals, only slightly less than those of the common amino-acids. The suggestion has been made that chelation with a metal plays a part in the therapeutic action of the drug, since 1-*iso*nicotinyl-1-methylhydrazine, which cannot give an anion and consequently does not form chelates, has very little antituberculous activity. The affinity of other hydrazides for heavy metals was determined; of two isomers of isoniazid, nicotinic hydrazide (which had no antituberculous activity) had the same order of affinity for metals as isoniazid; picolinic hydrazide (which has about 1/8th the activity of isoniazid) had 10^3 to 10^5 times the affinity for metals of isoniazid. So that the property of being able to form chelation compounds with metals is not the only factor concerned in the action of isoniazid. Nor does the replacement of nicotinamide in diphosphopyridine nucleotide by isoniazid explain its

antituberculous action, since cyanacetic hydrazide, which appears to act as an antitubercular in the same way as isoniazid, is not a structural analogue of nicotinamide. G. P.

***iso*Nicotinyl Hydrazide, Mode of Action of.** S. D. Rubbo, J. Cymerman-Craig, J. Edgar, G. N. Vaughan and D. Willis. (*Nature, Lond.*, 1956, **177**, 480.) The relatively insoluble complex of isoniazid formed by chelation with copper appeared to be as active as isoniazid or verazide, both in anti-



X′ X = a univalent anion

tuberculous activity *in vitro* and by the healing ulcer technique in guinea-pigs. With the healing ulcer method two injections of the complex effected 85 per cent. cure in three weeks and with three injections 99 per cent. cure was obtained in four weeks. However the compound had a much higher local and general toxicity in mice and guinea-pigs than had isoniazid. The suggestion was made that isoniazid is probably inactive in the absence of a chelating metal, antituberculous activity occurring after the formation of a chelate metal complex. G. P.

Pertussis Vaccines: Effect of Added Toxoids on Antigenicity. J. Ungar. (*Brit. med. J.*, 1956, **1**, 841.) This is the report of an investigation to determine whether or not the presence of either toxoid, diphtheria or tetanus, or of both, reduces the immunity response of mice to *H. pertussis* vaccines. Combined antigens that had been used for the immunisation of children, and having compositions based on earlier experiments on animals, were chosen. Two series of prophylactics were prepared by adding toxoids to each of two *H. pertussis* vaccines A and B, prepared on different occasions but otherwise similar. The following prophylactics were used: (1) Vaccine A 20,000 $\times$ 10^6 cells/ml. (2) Vaccine A plus diphtheria toxoid 25 Lf/ml. (3) Vaccine A plus diphtheria toxoid 25 Lf/ml., plus tetanus toxoid 2·5 Lf/ml. (4) Vaccine B 20,000 $\times$ 10^6 cells/ml. (5) Vaccine B plus diphtheria toxoid 25 Lf/ml. (6) Vaccine B plus diphtheria toxoid 25 Lf/ml., plus tetanus toxoid 2·5 Lf/ml. The pertussis vaccines were prepared from freshly isolated strains grown on Bordet-Gengou medium, killed with formalin and preserved in thiomersal. The added diphtheria and tetanus components were plain toxoids, purified by ammonium sulphate precipitation. The six products were tested three times concurrently for their ability to protect mice against intracerebral challenge. Similar mouse protection tests were carried out on a series of 12 plain *H. pertussis* vaccines, prepared from organisms grown for 48 hours on Bordet-Gengou medium, killed with formalin and standardised to 20,000 $\times$ 10^6 cells/ml. The results of these tests were compared with those on 16 different batches of a diphtheria-pertussis-tetanus prophylactic, prepared by the addition of both toxoids to *H. pertussis* vaccine suspensions similar to the 12 previously mentioned. Several of these tests on the two prophylactics were carried out concurrently, the animals being challenged at the same time with the same suspensions of virulent organisms. The results of the tests (which are given in detail in the paper) indicate that the antigenic response of mice to the two different *H. pertussis* vaccines investigated was not reduced by the addition of diphtheria toxoid or of

diphtheria and tetatus toxoids combined. This finding indicates that combined prophylactics will induce in children the same degree of protection against whooping cough as will a plain suspended vaccine. S. L. W.

Tetracyclines, Avidity of, for the Cations of Metals. A. Albert and C. W. Rees. (*Nature, Lond.*, 1956, **177**, 433.) Tetracycline, like chlortetracycline (aureomycin) and oxytetracycline (terramycin) showed high affinity for the cations of heavy metals. It is not known whether the antibacterial properties of the tetracyclines are related to their metal-binding properties as is the case with 8-hydroxyquinoline. However the binding properties are important since experiments have shown that alumina, given with the tetracyclines to prevent gastric irritation, completely inactivates them. G. P.

Tubercle Bacilli, Antituberculous Immunity Induced by Methanol Extracts of. D. W. Weiss and R. J. Dubos. (*J. exp. Med.*, 1956, **103**, 73.) Further confirmation was given of the increased resistance of mice to experimental tuberculosis (highly virulent bovine culture MV intravenously) by prior vaccination (intraperitoneally) with methanol extract of killed tubercle bacilli. Immunity was evident whether the challenge infective dose was large or small, causing a disease of short and long duration respectively. Two strains (avirulent H37Ra, and the attenuated strain BCG, substrain BCG-P) of tubercle bacilli were surface cultured, killed with phenol, washed with acetone, and then methanol extracted. Weight for weight, methanol extract possessed much less protective activity than the whole phenol-killed bacilli, but its primary toxicity was lower. The level of immunity elicited by whole cells and methanol extract was of the same order as that observed with living BCG. The duration of the methanol extract protective effect was greater (still present 62 days after vaccination) than that of living BCG-T, which gives only short duration immunity in mice. Also, the authors considered that the protective action of both whole phenol-killed bacterial bodies and their methanol extract, could be enhanced and prolonged by certain adjuvants; in particular, by an oil-arlacel mixture, and by highly purified typhoid somatic polysaccharide. G. P.

PHARMACOLOGY AND THERAPEUTICS

Acetazolamide in the Treatment of Epilepsy. B. Ansell and E. Clarke. (*Brit. med. J.*, 1956, **1**, 650.) Twenty-six epileptic patients were treated with acetazolamide; of these 23 were of the idiopathic type. There were 6 patients suffering from major epilepsy, 5 from minimal epilepsy, 4 from minor epilepsy, and 8 from mixed idiopathic epilepsy. The remaining 3 had symptomatic epilepsy of varying aetiologies and had resisted all therapy. 15 of the patients had acetazolamide alone over periods ranging from 4 weeks to 18 months. The majority were studied as out-patients. A dose of 125 mg. of acetazolamide twice a day was added to the previous medications in the first few cases. If improvement occurred and was sustained the other drugs were gradually eliminated. In most of those deriving no benefit the dose of acetazolamide was progressively increased and adapted to the individual until it was approximately 10 mg./kg. Excellent results (attacks completely dispelled) were obtained in 3 major, 2 minimal and 3 mixed epileptics; good results (attacks markedly decreased in frequency) were obtained in 1 of each of the major, minimal, minor and symptomatic groups, and in 2 of the mixed epileptics; slight results were obtained in 8 of the patients, and in 4 the treatment was of no value. Five of the patients complained of paræsthesia of the hands and feet, which usually persisted for about a week and recurred with an increase of dose. Excessive

drowsiness occurred in 4 patients (all had doses greater than 8 mg./kg.). One patient became depressed and irritable, but, on the other hand, behaviour difficulties decreased in 3 children. The authors conclude that acetazolamide may be of value as the sole therapeutic agent in the treatment of major epilepsy of moderate severity, in some cases of minimal epilepsy, and as adjuvant therapy in mixed idiopathic epilepsy. Repeated increase of dose is often necessary but as the drug is relatively non-toxic it can be used in doses of up to 20 mg./kg. The mode of action is unknown. It does not appear to depend on the production of a systemic acidosis. It is suggested that it may act specifically on the carbonic anhydrase in the epileptic brain. S. L. W.

Afroside B, Pharmacology of. M. J. Rand and A. Stafford. (*Austral. J. exp. Biol. med. Sci.*, 1956, **33**, 527.) Afroside B is a new crystalline cardiac glycoside obtained from *Gomphocarpus fruticosus*, growing in Queensland. In isolated perfused guinea-pig hearts a concentration of 1 in 7·5 million produced a positive inotropic response. A concentration of 1 in 10 million increased the strength of the isometric contraction of the cat papillary muscle. Toxicity experiments showed that by slow intravenous infusion in cats, anæsthetised with pentobarbitone, the mean lethal dose was 444 $\pm$ 5·6 μg./kg. Changes in the ECG were typical of those seen with other cardiac glycosides. In the guinea-pig, anæsthetised with urethane, the mean dose by intravenous infusion causing ventricular fibrillation was 477 μg./kg., compared with 469 μg. for digoxin and 245 μg. for ouabain. The doses to cause cardiac arrest were 600, 681 and 332 μg./kg. respectively. In the chick embryo heart, the potency compared with ouabain (= 1) was 2·09. In the guinea-pig afroside B was rapidly inactivated by passage through the liver *in situ* and the heart block produced by regular intra-atrial injections of adenosine were potentiated by non-toxic doses of afroside B. G. F. S.

Amiphenazole, Possible Mode of Action of. A. Shulman. (*Nature, Lond.*, 1956, **177**, 703.) Amiphenazole (2:4-diamino-5-phenylthiazole, Daptazole) has a mild respiratory stimulant action and has been used therapeutically to improve the respiration post-operatively and also in conditions such as pneumonia and asphyxia neonatorum. It has also been used in the treatment of barbiturate and morphine poisoning. When administered with morphine in cases of severe pain it minimises the degree of tolerance to the morphine and of addiction to the drug. It is effective orally and parentally, is free of side effects and it often improves the mental outlook of depressed patients. Since amiphenazole has such widespread effects in the body and since it has a very low toxicity the possibility that the drug might fit into some fundamental physiological process was investigated. As the structures of amiphenazole and the thiazole group of aneurine is similar and as aneurine is probably the only substance occurring naturally in the body which contains the thiazole nucleus, experiments were carried out in which rats were fed on an aneurine free diet and were given daily doses of amiphenazole and the pyrimidine part of aneurine in order to see if these two drugs would produce a substance capable of entering into aneurine metabolism. It was found that at suitable dose levels no signs of aneurine avitaminosis were apparent nine weeks after beginning the treatment, while all the control animals died by five weeks. Similarly aneurine deficiency could be reversed by the administration of amiphenazole and the pyrimidine part of the aneurine molecule. Such results suggest that amiphenazole may enter into the pathway of processes involving aneurine metabolism and that this may be at least a partial explanation of the mode of action of the drug. M. M.

Benactyzine Hydrochloride (Suavitil) in the Relief of Anxiety. E. B. Davies. (*Brit. med. J.*, 1956, **1**, 480.) Benactyzine hydrochloride is the hydrochloride of the diethylaminoethyl ester of benzilic acid, and has the formula:

$$HO{\cdot}C{\cdot}(C_6H_5){\cdot}_2COOCH_2{\cdot}CH_2{\cdot}N(C_2H_5)_2HCl.$$

It is claimed that the drug relieves anxiety, particularly in psychoneurotic patients and that no toxic effects are observed in therapeutic doses. (1–5 mg. up to 4 times a day.) It is rapidly eliminated, so that a dose of 4–5 mg. loses its effect after 3 to 5 hours. Moderate doses (1–4 mg.) produce a sense of divorce between outer reality and emotional reaction, which has been described as producing a barrier between the person and his problems. Larger doses (4–8 mg.) produce a more marked feeling of detachment, the muscles are relaxed, thoughts and feelings are retarded, and the power of concentration is felt to be diminished. There is a marked tendency to think of nothing and to react very slowly to stimulation from the outside world. With therapeutic doses the capacity to perform normal tasks may be little affected. It has little direct effect upon sleep, though it may have considerable indirect influence. This paper reports the use of the drug on 110 patients (56 men and 54 women); 25 were psychotics and 85 neurotics. It was used empirically as a means of relieving tension and anxiety, irrespective of the cause, in an attempt to assess its effect in all cases of tension. No controls were employed. Of the 110 patients, 67 were improved, 35 were unchanged, and 8 were worse, following a dosage of from 1–4 mg. three times a day. The drug is suitable for use with other sedatives, particularly phenobarbitone. A note of caution should be sounded concerning its use in patients with phobic obsessional disorders or feelings of depersonalisation or unreality. S. L. W.

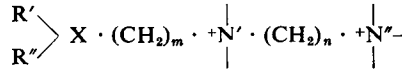
Benactyzine Hydrochloride as a Physical Relaxant. A. Coady and E. C. O. Jewesbury. (*Brit. med. J.*, 1956, **1**, 485.) The possible effect of benactyzine hydrochloride in relieving muscular rigidity, spasm or pain was investigated in a group of 80 neurological patients. No effect on muscle tone and no significant relief of symptoms were produced by a 2-weeks course of 2 mg. of benactyzine three times daily by mouth, and no temporary reduction of rigidity or of tendency to clonus was observed after individual doses. Although some patients reported diminished nocturnal spasms and cramps, greater mobility and confidence in walking, and increased general activity, these effects occurred almost equally both with benactyzine and inert control tablets. No systemic toxic effects were observed but transient side-effects occurred in 29 of 72 patients who received a dosage of 2 mg., and in all 8 patients who received 4 mg. The commonest side-effects were feelings of general apathy or detachment, and altered sensations in the limbs; other side-effects were dizziness, slight nausea, throbbing or tingling sensations, and blurred vision. The symptoms developed quickly and lasted from a few minutes to one and a half hours. With single oral dosage of more than 6 mg. normal control subjects showed increasing thought-blockage, impairment of concentration, and slowness and clumsiness in carrying out complicated procedures such as piano-playing. Because of these symptoms it would seem advisable that patients under treatment with the drug should not be allowed to drive. A striking suppression of the normal rhythm of the EEG was observed after subcutaneous injection of 5 and 7 mg. respectively in two normal subjects. S. L. W.

Cortisone Treatment of the Low-Salt Syndrome. I. G. Graber, P. Beaconsfield and O. Daniel. (*Brit. med. J.*, 1956, **1**, 778.) Post-operative patients

with a low plasma sodium and chloride usually respond well to the administration of salt. Occasionally abnormally low plasma sodium and chloride levels persist despite the establishment of positive salt-and-water balance. Details are given of three patients who developed a low-sodium syndrome following major surgical procedures and who failed to improve in spite of what was regarded as adequate replacement therapy. The condition was quickly remedied in all 3 patients by stopping administration of salt by mouth and administering cortisone acetate, 25 mg. every 6 hours. In 2 of the patients the plasma sodium and chloride returned to normal within 12 hours of commencing cortisone treatment. The rapid changes in plasma electrolytes following administration of cortisone in these cases is explained on the basis of cortisone altering cell permeability, allowing sodium and chloride to pass quickly from the cell into the plasma, thus restoring the normal plasma electrolyte picture and relieving intracellular œdema. This explanation is supported by the fact that cortisone administration was followed almost immediately by a greatly increased urinary output of sodium and a relatively diminished urinary output of potassium. S. L. W.

Ecolid, Action of, in Man. F. H. Smirk and M. Hamilton. (*Brit. med. J.*, 1956, **1**, 319.) The actions of Ecolid (4:5:6:7-tetrachloro-2(2-dimethylaminoethyl)*iso*indoline dimethochloride) a new hypotensive agent, have been studied and compared with pentolinium in 28 patients suffering from hypertension. The relative potency of the two drugs varied for each individual, but Ecolid appeared to be two to three times more potent than pentolinium. The effective oral dose was about fifteen times the parenteral dose. After a subcutaneous dose the blood pressure fall was maximal after one to two hours and was maintained for several hours. The effect on heart rate was slight and variable. The hypotensive action was greatest when standing and was increased by a meal. Patients showed a tolerance to Ecolid necessitating daily increases in dose in the early stages of treatment and there was a cross-toleration to pentolinium. Side effects observed were similar to those with other ganglionic blocking agents. The authors suggest that Ecolid merits further clinical trial. G. F. S.

Ganglion-blocking Agents, New Series of. D. W. Adamson, J. W. Billinghurst and A. F. Green. (*Nature Lond.*, 1956, **177**, 523.) Marked ganglion-blocking action was found in series of diquaternary-amino-carbinols (I), -alkenes (II), -alkanes (III), -nitriles (IV), -ethers (V), and esters (VI).



I; X = $C(OH)CH_2$ IV; X = $C(CN)CH_2$

II; X = C:CH V; X = CH:O

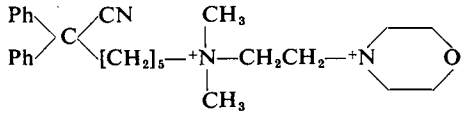
III; X = $CH{\cdot}CH_2$ VI; X = $CH{\cdot}CO{\cdot}O$

R′ and R″ = phenyl or *cyclo*hexyl groups.

N′ and N″ are fully substituted quaternary nitrogens.

Compounds I to III are related to series of spasmolytics, antihistamines and analgesics previously studied, e.g., tricyclamol, procyclidine, triprolidine and thiambutene; series IV is related to methadone, V to diphenhydramine and VI to the spasmolytic Trasentin. By introducing into the molecules a group consisting of two quaternary nitrogens linked by a short polymethylene chain, in place of the tertiary or quaternary nitrogens in the parent compounds,

ganglion-blocking activity was obtained in all the series, while the original types of activity were reduced or disappeared. Ganglion-blocking activity was tested for by antagonism of the pressor action of *N'N''*-dimethyl-*N''*-phenylpiperazinium, fall in blood pressure, blockade of vagal bradycardia, and augmentation of the pressor action of adrenaline and noradrenaline in cats and dogs. These effects were obtained with doses smaller than those necessary for blockade of transmission through the superior cervical ganglion of the cat. Some of the compounds were powerful inhibitors of gastric secretion in pyloric-ligated rats, in doses producing little mydriasis. The peristaltic reflex of isolated guinea-pig ileum was inhibited readily by the compounds. The main toxic action was associated with neuromuscular block, in doses up to 100 times ganglion-blocking doses. Some of the compounds were much more active ganglion-blocking agents than hexamethonium or pentolinium and action lasted longer. Of the compounds used successfully clinically in hypertension 356C54 (below) was one of the most promising.



Subcutaneous injection of an effective dose lowered blood pressure for 7 to 12 hours. Side effects were minimal, paralytic ileus or severe constipation being absent; gastric secretion and motility were inhibited suggesting a use in peptic ulcer therapy. G. P.

Mestinon Bromide in the Treatment of Myasthenia Gravis. J. E. Tether. (*J. Amer. med. Ass.*, 1956, **160**, 156.) Mestinon bromide (a dimethylcarbamate of 3-hydroxy-1-methyl pyridinium bromide) was given to 165 patients with myasthenia gravis for periods of from 3 to 17 months. The dosage requirements varied widely. Thirty-three per cent. of the patients took less than 200 mg. daily (in tablets containing 60 mg.), 30 per cent. took 200 to 399 mg., 29 per cent. took 400 to 1399 mg., and 8 per cent. took 1400 mg. or more. One patient took 6000 mg. of the drug as well as 1500 mg. of neostigmine, without apparent beneficial effect and without side-effects. Most of the milder cases required under 200 mg. daily, and obtained almost complete relief of symptoms. Patients requiring more than 1200 mg. daily did not obtain as good control of symptoms as those in the lower dosage groups. No organic toxic effects were noted regardless of the dosage, but when given in excess it produces, in addition to sweating, salivation and mild abdominal symptoms, "nicotinic" side effects, such as muscle fasciculations, blurring of vision with mild vertigo, and occasionally a "thick tongue" sensation, with dysarthria and dysphagia. These symptoms are usually accompanied by increased weakness. If they are ignored, and medication is continued, this weakness may include the muscles of respiration resulting in a cholinergic crisis. Occasionally, cholinergic weakness may precede all other signals of overdosage. In the majority of cases symptoms of overdosage are clear enough to serve as warning signals. The author considers Mestinon to be an advance in the treatment of myasthenia and to be preferred to neostigmine bromide because of its ability to provide effective smooth control of myasthenic symptoms without distressing side-effects or wide fluctuations in the intensity of the drug's action. S. L. W.

Primidone; Megaloblastic Anæmia during Therapy. R. H. Girdwood and J. A. R. Lenman. (*Brit. med. J.*, 1956, **1**, 146.) An account is given of a

patient who developed megaloblastic anæmia while receiving primidone and phenobarbitone for epilepsy. The patient had been receiving phenobarbitone ½ gr. (32 mg.) three times daily, and primidone 250 mg. twice daily for a period of seven months before admission to hospital. There was no response to injections of cyanocobalamin but a good response occurred to folic acid therapy. Tests for folic acid excretion gave no evidence of malabsorption of synthetic folic acid. Epilepsy is a common disorder and anticonvulsant drugs are used in large quantities; megaloblastic anæmia from the use of phenobarbitone alone has not been recorded and its occurrence after phenytoin or primidone therapy is very rare. It is possible, however, in view of the similarities in chemical structure that these two substances act as competitive inhibitors of some enzyme system normally involving folic acid as a co-factor. S. L. W.

Progesterone and 17α-Hydroxyprogesterone, Comparative Anti-œstrogenic Potencies of. E. Mardones, D. Jadrijevic and A. Lipschutz. (*Nature, Lond.*, 1956, **177**, 478.) Progesterone is known to prevent the induction by œstrogens of abdominal fibroid formation, myometrial growth and excessive luteinization. This antagonism of œstrogens is decreased by oxidation of the progesterone at the C(21), C(11) and C(17) positions, but evidence for loss of anti-œstrogenic potency in the C(17) compound has previously been indirect. Pellets of 17α-hydroxyprogesterone and œstradiol were implanted in castrated female guinea-pigs. Neither œstrogen-induced abdominal fibroids nor uterine growth was prevented by as much as 136 μg. of 17α-hydroxyprogesterone per day; 15 μg. of progesterone per day, in similar circumstances, had pronounced anti-œstrogenic activity. 11β-Hydroxyprogesterone, 11-ketoprogesterone and deoxycorticosterone also were more active than 17α-hydroxyprogesterone. G. P.

Tricyclamol, Studies on. W. H. Bachrach and H. Schapiro. (*Amer. J. med. Sci.*, 1956, **231**, 192.) The physiological and clinical effects of trycyclamol sulphate (1-*cyclo*hexyl-1-phenyl-3-pyrrolidino-1-propanol methyl sulphate Elorine sulphate), an anticholinergic drug, have been studied in 150 individuals. Doses of 10 to 20 mg. parenterally and 150 to 200 mg. orally, inhibited gastrointestinal motility and both normal and histamine induced secretion of gastric juice. Oral doses up to 250 mg. did not prevent the gastric secretory response to a standard meal or to injected insulin. Clinically, tricyclamol sulphate did not relieve functional dyspepsia or pancreatitis. In peptic ulcer therapeutic results were good in 60 per cent. of patients receiving in addition adequate doses of antacids. Side effects, such as dryness of the mouth, were present, but were rarely troublesome at therapeutic doses. About 10 per cent. of patients showed an idiosyncrasy to the drug. Its actions are comparable to the natural and synthetic anticholinergic drugs. G. F. S.

Triiodothyronine; Metabolic and Therapeutic Effects. T. F. Frawley, J. C. McClintock, R. T. Beebe and G. L. Marthy. (*J. Amer. med. Ass.*, 1956, **160**, 646.) Fourteen myxœdematous patients were observed over a two-year period during which four types of medication were compared as follows: (1) 3:5:3′-DL-triiodothyronine, in a total daily dose of from 25 to 400 μg.; (2) L-triiodothyronine, in a daily dose of from 100 to 200 μg.; (3) L-thyroxine sodium, in a daily dose of 100 to 500 μg.; (4) desiccated thyroid, in an average daily dose of 86 mg. The four substances were all effective in raising the body temperature, accelerating the pulse, increasing the rate of oxygen consumption, decreasing the body weight, reducing the serum cholesterol and carotenoid levels, and improving the mental state of the patient. With DL-triiodothyronine the average daily dose to maintain euthyroidism is about 200–250 μg.; with L-tri-

iodothyronine a dose of 75–100 μg. is sufficient. This suggests that the effectiveness of the DL-form is due to its L-triiodothyronine content. The equivalent dosage of L-thyroxine sodium was between 200–300 μg. daily, and of thyroid extract was between 96–192 mg. Side-effects attributed to triiodothyronine included palpitation, angina, dyspnœa and headache. An unexpected syndrome was the sudden and marked relapse following the withdrawal of triiodothyronine. Within 24 hours patients complained of being weak and tired and of a return of their hypothyroid symptoms. The cause of this rapid loss of effectiveness is related to the speed with which the compound disappears from the tissues. The duration of activity after cessation of treatment or reduction in dosage is judged to be less than 3 days and in order to avoid a relapse it is necessary to start therapy with thyroid extract or thyroxine several days prior to the withdrawal of the triiodothyronine. On the other hand, triiodothyronine has the advantages that it is a chemically pure synthetic compound not requiring standardisation, that it acts rapidly in very small doses, and that it produces a calorigenic response when the patient's condition is refractory to thyroid extract or thyroxine. S. L. W.

Zoxazolamine for Cerebral Palsy in Children. E. H. Abrahamsen and H. W. Baird, III. (*J. Amer. med. Ass.*, 1956, **160**, 749.) After a preliminary trial in 10 children who had a marked increase in muscle tone of the extremities and were severely mentally retarded, zoxazolamine (Flexin) was given to 28 children who had in addition other abnormalities including orthopædic deformations, behaviour disorders, convulsive disorders, or growth failure. Initial dosage was 50 mg./kg. daily in 3 or 4 divided doses by mouth, the amount being increased by 25 to 50 per cent. at intervals of 1–2 weeks until side effects were observed or muscular relaxation was demonstrable. The dose of the drug necessary to produce a definite decrease in muscle tone was from 30 to 140 mg./kg. daily. The drug was given for from 10 to 210 days and a decrease in muscle tone was demonstrable in every patient, with definite clinical improvement in 15. An effective dose produced relaxation within an hour, the effect reaching a peak within 2 hours and waning within 4 hours. Occasionally some relaxation was still present after 24 hours. Side effects occurred in 15 patients; they included a burning taste, anorexia, vomiting, hypotonia and bleeding from a duodenal ulcer. Children who chewed the tablets complained of the taste and in these cases the crushed tablet was given in honey or treacle. H. T. B.

Zoxazolamine in Rheumatic Diseases. R. T. Smith, K. M. Kron, W. P. Peak and I. F. Hermann. (*J. Amer. med. Ass.*, 1956, **160**, 745.) Zoxazolamine (Flexin) was tried in 100 patients with rheumatic disease in whom acute or chronic fibrositic symptoms predominated, including rheumatoid spondylitis, fibrositis, peripheral rheumatoid arthritis, acute torticollis and post-traumatic muscle spasm of the low back. The usual dose was 500 mg. 3 or 4 times a day in the form of tablets. In 41 patients the response was excellent, relief of the stiffness occurring within 20–30 minutes and continuing throughout the day. In 44 the response was good, only mild stiffness persisting 30–60 minutes after the dose. 7 patients claimed slight benefit. The best over-all relief of muscle spasm occurred in patients with rheumatoid spondylitis. Toxic effects occurred in 43 patients, the most common being gastrointestinal irritation and disturbance of equilibrium. Fever, burning of the eyes, and skin rash also occurred. In 9 the symptoms gradually disappeared without altering the dose and 21 tolerated half the previous dose, but in the remainder treatment had to be discontinued. H. T. B.

Zoxazolamine in the Treatment of Spasticity. M. Rodriguez-Gomez, A. Valdes-Rodriguez and A. L. Drew. (*J. Amer. med. Ass.*, 1956, **160**, 752.) Zoxazolamine (Flexin) is a muscle relaxant resembling mephenesin in acting centrally; it appears to exert a somewhat selective depressing effect on subcortical and spinal polysynaptic pathways. The compound was given to 70 patients with increased muscle tone, of whom 35 were followed sufficiently closely and for a long enough time to permit evaluation. The patients belonged to two groups; in one the spasticity resulted from interruption of the corticospinal pathways at spinal cord levels while in the other the spasticity was secondary to disease above the spinal cord. 18 patients were in the first group, 10 suffering from multiple sclerosis, 6 from transverse myelitis and 2 from unclassified spinal cord disease. Of these, 14 showed undoubted reduction in spasticity. Patients with multiple sclerosis were given 500 mg. 3 to 5 times a day and improvement occurred in all except two within a period varying from a few days to 4 weeks. 5/6 of the transverse myelitis cases also showed marked improvement. The second group of patients responded less satisfactorily. In one case of paralysis agitans treatment with zoxazolamine noticeably improved rigidity and voluntary movement but no change in tremor was observed; in two other cases there was no improvement. Drowsiness and mild gastric irritation were the only side effects observed. H. T. B.

BACTERIOLOGY

Nicotin Hydrazide, Effect of, on the Oxidative Metabolism of *Mycobacterium tuberculosis* var. *bovis* BCG. P. Meadow and R. Knox. (*J. gen. Microbiol.*, 1956, **14**, 414.) This paper reports studies on the effects of isoniazid on the oxidation of acetate in the Warburg apparatus by mycobacteria and by other organisms. Only oxidation by the mycobacteria was found to be inhibited by isoniazid. *Myco. tuberculosis* var. *bovis* BCG and *Myco. tuberculosis* var. *hominis* were inhibited irrespective of the inclusion of glucose or glycerol in the medium, whereas *Myco. smegmatis* was inhibited only when grown in the absence of both glycerol and glucose. *Staph. aureus*, *B. cereus* and *E. coli* were not inhibited under any growth condition used. The acetate inhibition system was studied in further detail with BCG, when it was found that inhibition of acetate oxidation was not altered by varying the medium on which the organisms were grown. The concentration of isoniazid required to give 50 per cent. inhibition was found to depend on the cell concentration of BCG, the quantities of isoniazid required being related to sensitivity as determined by the test tube method. Reputed antagonists of the action of isoniazid: pyridoxine, manganous chloride, biotin, oleic acid derivatives, hæmin and catalase, were tested on the inhibition of acetate oxidation by BCG None was effective. Several disinfectants were found to cause complete inhibition of acetate oxidation by BCG, e.g., phenol (0·01 per cent.). Lastly, mixtures of antituberculous drugs as inhibitors of the acetate system were studied. Mixtures of subinhibitory concentrations of isoniazid with streptomycin, *p*-aminosalicylic acid or terramycin or of streptomycin with *p*-aminosalicylic acid all gave 50 per cent. inhibition of acetate oxidation by BCG. Mixtures of isoniazid with aureomycin, tetracycline, thiosemicarbazone and cyanacetic acid hydrazide were not effective. The authors suggest that their method might be applied usefully to studies of the actions of other drugs or mixtures of drugs, particularly since the selection of resistant strains is largely eliminated by the short duration of the experiments. B. A. W.