ABSTRACTS OF PAPERS PUBLISHED IN OTHER JOURNALS

CHEMISTRY

ANALYTICAL

Adrenaline and Noradrenaline Solutions, Analysis of. L. H. Welsh. (*J. Amer. pharm. Ass., Sci. Ed.*, 1955, **44**, 507.) Solutions of adrenaline salts were assayed by converting the amine to its triacetyl derivative with the aid of acetic anhydride and sodium bicarbonate, extracting the acetyl derivative with chloroform, removing the solvent and weighing. By determining the optical rotation of a solution of the triacetyl derivative, the amount of racemisation which had occurred in the adrenaline solution was estimated and taken into account in calculating the potency of the preparation. Good recoveries were obtained by this method and the results agreed well with potencies determined by the U.S.P. XIV biological assay, using dogs. The method was also applicable to noradrenaline. For the determination of noradrenaline present as an impurity in solutions of adrenaline, the triacetyl derivatives were separated by partition chromatography on Celite columns, using water as the stationary phase and benzene as the mobile phase. The separated triacetyl derivative of noradrenaline was hydrolysed to the base which was estimated colorimetrically. G. B.

Barbiturates, Chromatography of. E. Hjelt, K. Leppänen and V. Tamminen. (*Analyst*, 1955, **80**, 706.) Barbiturates are separated by ascending-paper chromatography on Whatman No. 1 paper impregnated with M potassium nitrate, *n*-butanol–pentanol–ammonia being used as the solvent. The paper is kept in a solvent atmosphere for at least 6 hours, the chromatography time usually being 18 hours; mixtures are kept for 12 to 14 hours in a solvent atmosphere. After development, the dried paper is sprayed with a 1 per cent. solution of cobalt nitrate in absolute ethanol, dried again and then held in ammonia vapour when 50 μg. quantities of barbiturates show as a violet or reddish colour. For smaller quantities (5 to 10 μg.) the paper is sprayed with a solution containing 200 mg. of copper sulphate, 2 ml. of pyridine and 20 mg. of quinine per 100 ml. of water and the dried paper is then held in hydrochloric acid vapour. In ultra-violet light, the barbiturates are visible against the fluorescent background either as dark blue spots or circles; thiopentone is indicated by a yellow-green colour in visible light. Treatment with potassium permanganate then indicates unsaturated barbiturate derivatives. Using *n*-butanol–pentanol–ammonia not more than 5 days old, at 22° C., the following R_F values were found: barbitone 0·33, phenobarbitone 0·42, allobarbitone 0·49, cyclobarbitone 0·57, hexobarbitone 0·71, amylobarbitone 0·80, pentobarbitone 0·80, and thiopentone 0·83. R. E. S.

Digitoxin and Digoxin, Identification from their Acetyl Compounds by Means of Paper Chromatography. S. Rohatgi. (*J. Amer. pharm. Ass., Sci. Ed.*, 1955, **44**, 428.) Digitoxin, α-acetyldigitoxin and β-acetyldigitoxin were separated by paper chromatography using the descending technique with propylene glycol as the stationary phase and a mixture of 9 parts of benzene with 1 of chloroform as the mobile phase. α-Acetyldigitoxin moved the most rapidly and could be separated by running the chromatogram for about 24 hours. For the separation of digitoxin and β-acetyldigitoxin about 48 hours was required.

In an alternative separation which was completed in about 5 hours, a mixture of equal volumes of chloroform and benzene was used as mobile solvent, with formamide as the stationary phase, but in this case the spots were not so well defined. Complete separation of digoxin and α-acetyldigoxin was effected in about 20 hours, using formamide as the stationary phase and a mixture of 3 parts of benzene with 7 of chloroform as the mobile phase. The spots were made visible by spraying the paper with *m*-dinitrobenzene solution, drying and spraying with sodium hydroxide solution. Digitoxin, α-acetyldigitoxin, digoxin and α-acetyldigoxin gave purple spots, whilst those due to β-acetyldigitoxin were deep blue. G. B.

3 : 5-Dinitro-*o*-cresol, Determination of. M. L. Fenwick and V. H. Parker. (*Analyst*, 1955, **80**, 774.) The method of determination of 3 : 5-dinitro-*o*-cresol in which an alkaline ethyl methyl ketone extract, containing the yellow sodium salt of DNOC, is compared photometrically with a similar extract of a standard solution of DNOC, has been found inadequate, in that β-carotene, also, is partly extractable by ethyl methyl ketone. Two ways of overcoming this difficulty are described. In the first, for cow's blood, the extraction procedure is that of Parker (*Analyst*, 1949, **74**, 646), the method depending upon the fact that, whereas the sodium salt of DNOC is bright yellow, the free acid is almost colourless in ethyl methyl ketone; the optical density of β-carotene at 430 mμ, however, is the same in acid or alkaline solutions. This method was not applicable to the determination of DNOC in locusts because of the production of highly stable emulsions after extraction with ethyl methyl ketone. In this method, the locust is homogenised in a mixture of chloroform and trichloroacetic acid. An aliquot of the chloroform extract is shaken with sodium carbonate solution, which extracts the DNOC but not the carotene. A portion of the carbonate extract is shaken with ethyl methyl ketone in the presence of sufficient sodium chloride to "salt out" the DNOC. The optical density at 430 mμ of the ketone solution is then compared with a standard curve. R. E. S.

Reserpine, Analytical Methods for. W. H. McMullen, H. J. Pazerda, S. R. Missan, L. L. Ciaccio and T. C. Grenfell. (*J. Amer. pharm. Ass., Sci. Ed.*, 1955, **44**, 446.) The following methods were employed successfully for the assay of reserpine in tablets and other pharmaceutical preparations. (1) A sample of about 10 mg. was dissolved in chloroform and extracted with 0·01 M hydrochloric acid to remove reserpic acid, followed by a 1 per cent. solution of sodium bicarbonate to remove trimethoxybenzoic acid. The ultra-violet absorption of the solution was determined at 295 and 268 mμ, after further dilution of the solution with chloroform. The ratio of the absorbancies at these wavelengths (1·83) served to identify the solute as reserpine. The concentration of reserpine was calculated by reference to a standard curve. The quantity of reserpine in the preparation, which had decomposed into trimethoxybenzoic and reserpic acids was calculated from the absorbancies of the sodium bicarbonate and hydrochloric acid solutions. (2) A sample of about 1 mg. was dissolved in chloroform and extracted with a 1 per cent. solution of sodium bicarbonate. The chloroform solution was evaporated to small bulk, and the remaining chloroform removed after the addition of M acetic acid. The solution was heated with concentrated sulphuric acid, cooled and the light absorption determined at 380 mμ. The quantity of reserpine was calculated by using a standard curve based on measurements with a standard solution of reserpine in M acetic acid, similarly treated. Reserpine was separated from serpentine, ajmaline, ajmalicine, yohimbine, reserpic acid hydrochloride and other sub-

stances by paper partition chromatography. A system employing 2 per cent. of acetic acid in propylene glycol as the stationary phase and equal quantities of benzene and *cyclo*hexane as the mobile phase yielded sufficient quantities of reserpine for absorption measurements. G. B.

Reserpine in Tablets, Identification and Determination of. D. Banes. (*J. Amer. pharm. Ass., Sci. Ed.*, 1955, **44**, 408.) Reserpine is feebly basic and can be separated from more strongly basic alkaloids by extraction from acidic solutions with chloroform. Dilution of the chloroform solution with *iso*octane enables the reserpine and other weak bases to be extracted with a dilute solution of citric acid. The quantity of reserpine in this solution may be determined by adding vanillin and sulphuric acid and measuring the light absorption at 532 mμ at intervals until it reaches a maximum. The result is calculated by comparison with the absorption of a solution of a standard preparation of reserpine, similarly treated. Reserpine may also be assayed by hydrolysis followed by determination of the reserpic and trimethoxybenzoic acids produced. Reserpic acid is estimated colorimetrically after treatment with vanillin and sulphuric acid (as for reserpine) and trimethoxybenzoic acid is determined by ultra-violet spectrophotometry at 262 mμ using a standard solution of trimethoxybenzoic acid as a basis of comparison. Samples of reserpine for analysis must be freed from reserpic or trimethoxybenzoic acids occurring as impurities or high results will be obtained. When the result of the trimethoxybenzoic acid assay is significantly greater than that of the vanillin colorimetric assay, this indicates the presence of decomposed reserpine or recanescine in the sample. The method is suitable for the assay of reserpine tablets. G. B.

Surface Active Agents, Analysis of. V. W. Reid, T. Alston and B. W. Young. (*Analyst*, 1955, **80**, 682.) The identification of surface active agents can be simplified by the determination of ultra-violet absorption between 210 to 350 mμ followed by tests to show ionic character and the presence or absence of nitrogen; examination also for the presence of sulphur or phosphorus is sometimes necessary. Details are given of the absorption characteristics of surface active agents in four groups: anionic compounds with nitrogen absent including alkylbenzenesulphonates, alkylnaphthalenesulphonates, tetralinsulphonates, arylbenzenesulphonates, alkyl sulphates and conventional soaps; non-ionic compounds with nitrogen absent including phenols and cresols, naphthols, resin acids, fatty acids and alcohols; anionic compounds containing nitrogen including aniline derivatives and alkylolamine soaps; cationic compounds containing nitrogen including quaternary ammonium compounds, quaternary base with a pyridine nucleus, quaternary base with an *iso*quinoline nucleus and aliphatic amino compounds. When mixtures of surface-active agents are being examined greater emphasis should be placed on the characteristics of the ultra-violet spectrogram since chemical tests are confusing. R. E. S.

ORGANIC CHEMISTRY

Collagen, Polypeptide Chain Configuration of. P. M. Cowan, S. McGavin and A. C. T. North. (*Nature, Lond.*, 1955, **176**, 1062.) The main features of the polypeptide chain configuration of collagen are indicated by consideration of the high-angle X-ray diffraction pattern, the amino-acid composition and sequence analysis, and the structure of poly-L-proline. The high-angle X-ray diffraction pattern is consistent with a system of hexagonally packed rods, consisting of atom sets which may be one or more amino-acid residues. The changes in the pattern when the fibre is stretched suggest a helical structure.

Consideration of the general form of the intensity distribution to be expected from a number of simple helical structures, and comparison with the observed high-angle X-ray pattern shows that in collagen the single helical form with a period of 28·6 Å containing either three or seven turns, and ten atom sets is the most likely. The measured density of dry collagen fibres shows that there are probably three amino-acid residues in the 2·86 Å atom set, and analysis of the X-ray diagram suggests that the observed helix form could arise from a unit of three chains, each with one residue in 2·86 Å, and coiled round one another. Examination of the peptides derived from collagen by hydrolysis suggests that there is not a rigid repeated sequence of amino-acids, though the sequence proline-hydroxyproline-glycine has been observed. All three amino-acids occur in other sequences, though hydroxyproline is always associated with glycine. The amino-acids are found in the proportions glycine (1/3 of total), proline (1/8) and hydroxyproline (1/10). The hypothesis is put forward that the prolyl-hydroxyprolyl-glycyl sequence is concentrated in one of the three chains conferring a special configuration, with the remaining two chains crystallising about the first. Poly-L-proline also has a helical structure in which the amino-acid residues are related by an exact threefold screw axis, with repeat spacing of 3·12 Å, which suggests that the chain has a similar configuration to that of collagen. The high specific *lævo*-rotation of both suggests that the minor helixes of these structures are left-handed. It is suggested that the three chains are linked together by NH . . . O, and possibly OH . . . O, hydrogen bonds. J. B. S.

α-Corticotrophin, Amino-acid Sequence of. C. H. Li, I. I. Geschwind, R. D. Cole, I. D. Raacke, J. I. Harris and J. S. Dixon. (*Nature, Lond.*, 1955, **176**, 687.) The complete amino-acid sequence of α-corticotrophin is proposed, based on data from the structure of peptide fragments isolated from enzymatic and partial acid hydrolysates of the hormone. From the results of limited digestion with crystalline pepsin followed by chromatographic separation of the peptides, the following sequence was deduced for the carboxyl end of α-corticotrophin: asp.glu.ala.ser.glu.ala.phe.pro.leu.glu.phe. The following peptides were isolated by means of paper chromatography and paper electrophoresis from the tryptic digest of α-corticotrophin: ser.tyr.ser.(met.glu.his.phe)arg; try.gly.lys.pro.val.gly.lys.; lys.arg; lys.arg.arg; arg.pro.val.lys; and val.tyr.pro. ala.gly.glu(asp_2.glu_3.ala_2.ser.phe_2.pro.leu). Other peptides were obtained from the products resulting from the action of chymotrypsin on α-corticotrophin and from the partial acid hydrolysis of the DNP-derivative of this substance. The complete sequence is ser.tyr.ser.met.glu.his.phe.arg.try.gly.lys.pro.val.gly.lys.lys. arg.arg. pro.val.lys.val.tyr. pro.ala.gly.glu.asp.asp.glu.ala.ser.glu.ala.phe.pro.leu. glu.phe. A. H. B.

BIOCHEMISTRY

GENERAL BIOCHEMISTRY

6-Aminonicotinamide, a Potent Nicotinamide Antagonist. W. J. Johnson and J. D. McColl. (*Science*, 1955, **122**, 834.) A potent nicotinamide antagonist, 6-aminonicotinamide, was discovered during the course of investigation into the inhibition of sulphonamide acetylation. The LD50 for mice is 35 mg./kg. as compared with 305 mg./kg. of 3-acetylpyridine. Nicotinic acid (50 mg./kg.) increased the LD50 of 6-aminonicotinamide eight-fold although it was ineffective against 3-acetylpyridine. Tryptophan also afforded some protection against the new antagonist. Liver homogenates from mice injected intraperitoneally

72 hours previously with 100 mg./kg. of 6-aminonicotinamide and 25 mg./kg. of nicotinic acid had only 30 per cent. of the oxygen uptake of homogenates from untreated controls. The addition of either DPN or oxidisable substrate greatly increased the rate of uptake and addition of both together returned the rate almost to normal. No appreciable change in oxygen uptake was observed when 6-aminonicotinamide was added to normal liver homogenates *in vitro*. It seems probable that the toxicity of 6-aminonicotinamide may be due to the formation of an inactive DPN analogue with consequent depletion, in certain tissues, of DPN. Involution of the spleen, one of the pathological changes seen with 6-aminonicotinamide poisoning, may be related to the high rate of analogue formation by this organ. G. P.

BIOCHEMICAL ANALYSIS

Oxytocin and Vasopressin, Partition Chromatography of. P. G. Condliffe. (*J. biol. Chem.*, 1955, **216**, 455.) Separation of natural beef and hog oxytocin and vasopressin to a pure state by counter-current distribution requires material from the pituitary glands of some several thousand animals. Development of a chromatographic method has reduced the number of glands necessary for a suitable yield of the purified hormones to about 50 to 100 beef or 200 to 400 hog glands. Partition columns with diatomaceous earth as supporting phase and 2-butanol-dilute acetic acid as solvent were used. Distribution of peptide material in the column effluent fractions was determined with modified Folin phenol reagent. Ultra-violet absorption at 275 mμ of the fractions was compared with oxytocic activity assayed on chicken blood pressure and pressor activity on anæsthetised rats injected with dibenamine. The purity of the hormones obtained by this method was not as great as with counter-current distribution, but the method offers a practical solution to the problem of separation and characterisation of human posterior pituitary hormones. G. P.

Plasma Bilirubin, Determination of. J. H. Graham. (*Amer. J. med. Sci.*, 1955, **230**, 633.) The method utilises heparinised capillary tubes to collect blood from the toe or heel, and is particularly suitable for children. Sufficient plasma is obtained for direct reading as well as total bilirubin and simultaneous estimations of the hæmatocrit are possible. The method can also be used for the collection of plasma for the determination of plasma electrolytes. Heparinised capillary tubes 75 mm. long are used. They are filled approximately to two-thirds with blood and sealed at one end with a microburner. After centrifuging for 4 minutes at 11,000 r.p.m. the tubes are broken at the junction of the plasma and packed cells, and the plasma is blown into a small watch glass. To 0·1 ml. of plasma add 0·9 ml. of distilled water, and transfer 0·1 ml. of the diluted plasma to each of two microcuvettes of a spectrophotometer. To each microcuvette add 0·5 ml. of methanol, 0·1 ml. of a solution of sulphanilic acid (1g. dissolved in 15 ml. of conc. hydrochloric acid and diluted to 1 litre with water), and 0·1 ml. of freshly prepared diazo reagent. Allow to stand for 30 minutes and read the percentage transmission at 540 mμ and obtain the bilirubin values from a standard calibration curve. G. F. S.

Urinary Indoles, Paper Chromatography of. J. P. Jepson. (*Lancet*, 1955, **269**, 1009.) The method described can be applied directly to urine without any preliminaries and has been used during the past three years to study cases of carcinoid, phenylketonuria, mental and nervous disorders, and Hartnup disease, and is suitable for the routine screening of urine. The urine, applied at an origin on a 10-in. square paper on a frame is submitted to two-way chromatography:

firstly, in an ascending basic solvent (*iso*propanol-ammonia) and secondly in the right-angle direction in an acidic solvent (butanol-acetic acid). Indoles are revealed on the dried paper by dipping it through a modified Ehrlich reagent (*p*-dimethylaminobenzaldehyde in hydrochloric acid-acetone). The position of the resulting spots, their rate of appearance and fading and their differing colours serve to identify the indoles and give a rough guide to the amounts. The amount of urine needed to obtain an adequate chromatogram or assay must be found by trial but the method is such that 100 μl. of normal urine will show very little in the way of Ehrlich-reacting substances except urea and indican. This volume of urine from a case of metastasing carcinoid will show an immense reaction for 5-hydroxy-indolyl-acetic acid, a slight reaction for its sulphate ester, and traces of other unidentified indoles; similarly urine from a phenylketonuric will react strongly for indolyl-acetic acid and indolyl-lactic acid. S. L. W.

CHEMOTHERAPY

Albomycin, Recent Studies on. G. F. Gause. (*Brit. med. J.*, 1955, **2**, 1177.) Albomycin, a new antibiotic, has been manufactured during recent years by the pharmaceutical industry of the Soviet Union. It was obtained by Dause and Brazhnikova in 1951 from cultures of a new species of streptomycetes, *Actinomyces subtropicus*. Albomycin is a basic substance and forms salts with various acids. Chemically pure sulphate of albomycin is in the form of an amorphous red powder, easily soluble in water, slightly soluble in methanol, but insoluble in other organic solvents. It is effective against a variety of organisms and particularly against staphylococci resistant to other antibiotics; its action is about ten times as strong as penicillin. Albomycin is pharmacologically inactive; intravenous injections of large doses in animals do not affect the heart, blood pressure or respiration. It is devoid of cumulative toxicity and pyrogenic action and no local reactions occur when it is injected subcutaneously or intramuscularly. Intrathecal injection is safe and is not accompanied by any side-reaction. Complete absence of toxicity of the drug for man has been proved by extensive clinical practice over some years. A remarkable feature is the formation of a reversible complex between albomycin and serum proteins which facilitates its circulation in the body. Albomycin has proved effective in the treatment of pneumonia, especially in young children, in the septic complications of dysentery and measles, and in meningitis due to penicillin-resistant pneumococci. It has also been used in the treatment of peritonitis and other surgical infections and for penicillin-resistant prostatitis and gonococcal urethritis. It has been found very effective in the treatment of relapsing fever due to *Sp. sogdianum*, the dose being 3 million units intramuscularly twice daily for 7 to 12 days. Animal experiments indicate that albomycin is synergistic in combination with penicillin or streptomycin. S. L. W.

Filipin, an Antifungal Antibiotic: Isolation and Properties. G. B. Whitfield, T. D. Brock, A. Ammann, D. Gottlieb and H. E. Carter. (*J. Amer. chem. Soc.*, 1955, **77**, 4799). A new potent antifungal antibiotic, filipin, was obtained from the mycelium and culture filtrates of a previously unreported actinomycete, *streptomyces filipinensis*, found in a sample of Philippine soil. It is yellow neutral compound whose analysis best fits the empirical formula $C_{30}H_{50}O_{10}$. It is non-aromatic and has been characterised as a conjugated polyene. It is susceptible to autoxidation and particularly so when exposed to light. It is stable under nitrogen even when exposed to direct sunlight, and is stable in the dark in air at refrigerator temperatures. Filipin is relatively stable in very dilute solutions in ethanol. Fusion studies indicate that it exists in two

solid modifications; it undergoes transition to a second form at 147° C. and this second form melts at 195 to 205° C. with decomposition. It has a specific rotation of $[\alpha]_D^{22}$ − 148·3 (*c* 0·89 in methanol) and gives a positive Molisch test and negative ninhydrin, Benedict, anthrone, ferric chloride and 2:4-dinitrophenylhydrazine reactions. When concentrated methanolic or ethanolic solutions of filipin are stood at 4° C., a transition to a white crystalline substance ($C_{30}H_{50}O_{11}$) takes place. This product has no antifungal activity, but it is still a polyene as evidenced by its ultra-violet absorption spectrum and hydrogenation studies. A. H. B.

Sarcolysine (DL-*p*-Di(2-chloroethyl)aminophenylalanine), Anti-tumour Activity of. L. F. Larionov, A. S. Khokhlov, E. N. Shkodinskaja, O. S. Vasina, V. I. Troosheikina and M. A. Novikova (*Lancet*, 1955, **269**, 169.) Sarcolysine was prepared by reducing acetamido-*p*-nitrobenzylmalonic ester with hydrogen and Raney nickel. The amino compound was treated with an excess of ethylene oxide in aqueous ethanol in sealed tubes at 85 to 90° C., the product being acetamido-*p*-di(2-hydroxyethyl)aminobenzylmalonic ester. This was treated with thionyl chloride in chloroform and converted to DL-*p*-di(2-chloroethyl)aminophenylalanine hydrochloride by heating under reflux with hydrochloric acid. The following analogues were also prepared:—DL-*p*-di(2-bromoethyl)aminophenylalanine, DL-*p*-dimethylaminophenylalanine and DL-*p*-diethylaminophenylalanine. Sarcolysine was tested in rats infected with the transplantable rat sarcoma 45, a strain developed from a tumour induced by 9:10-dimethyl-1:2-benzanthracene. Three injections of 5 mg./kg. given intraperitoneally at intervals of 72 hours, or a single injection of 15 mg./kg. were sufficient to cause complete regression of the tumours. No toxic effects were observed unless the dosage was increased to 10 mg./kg. repeated at intervals of 72 hours. Sarcolysine also caused inhibition of the growth of another rat spindle-cell sarcoma (strain M1) and of mammary adenocarcinoma in mice (strain RSM), but complete regression did not occur with these tumours. Sarcolysine is also being studied for its action against neoplastic diseases. G. B.

PHARMACY

NOTES AND FORMULÆ

Ergot, Preparation and Stabilisation of Extracts. F. Gstirner and H. O. Müller. (*Arch. Pharm. Berl.*, 1955, **288**, 393.) By using ethanol (70 per cent. by volume) containing 0·5 to 1 per cent. of tartaric acid it is possible to extract 90 per cent. of the alkaloids from ergot by using a quantity of a menstruum only double that of the drug. Thus a 1:2 fluid extract can be prepared with no need for any working up of after-runnings. Such extracts, prepared from non-defatted drug, contain up to 1 per cent. of fat according to the strength of the ethanol used, but this does not interfere with the stability of the product. Stabilisation tests showed that the decomposition of the alkaloids is independant of the hydrogen ion concentration. The addition of 1 per cent. of ascorbic acid gave an extract which is stable for 3 months, with 2 per cent. for 4 months. An extract prepared with 45 per cent. ethanol and containing 1 per cent. of ascorbic acid, and gassed with nitrogen, was stable for 10 months, but in the case of a similar experiment with 70 per cent. ethanol the stability was quite low. In the latter case 2 per cent. of ascorbic acid and bubbling with nitrogen gave a stability of 7 months. Cysteine hydrochloride (1 per cent.) had a stabilising action only in 96 per cent. ethanol, and even without nitrogen treatment there was no appreciable change in strength after 10 months. G. M.

Emulsification with Ultrasonic Waves. H. M. Beal and D. M. Skauen. (*J. Amer. pharm. Ass., Sci. Ed.*, 1955, **44**, 487, 490.) Emulsions were prepared experimentally by submitting the ingredients to the effects of ultrasonic vibrations in several exposure chambers. The emulsions were examined microscopically and evaluated by means of globule counts. Good results were obtained by the use of an exposure chamber consisting of a pyrex test tube the bottom of which had been replaced by a threaded brass collar, the tube being closed by a diaphragm of aluminium, copper, cellulose acetate or brass. Similar results were obtained with a flat-bottomed tube of cellulose acetate with a wall thickness of 0·5 mm. The best results were obtained by placing the exposure chamber so that the bottom was a definite number of half-wavelengths from the crystal generating the ultrasonic frequency. Under these conditions the maximum energy entered the chamber. Solutions of polyethylene glycol 400 monostearate, tragacanth and hard soap showed significant losses in viscosity when submitted to ultrasonic waves, and this would appear to be a disadvantage when they are used for the preparation of emulsions by this method. The viscosity of solutions of acacia, sodium lauryl sulphate and polysorbate was not affected by ultrasonic vibrations. Emulsions of light liquid paraffin, liquid paraffin, cottonseed oil and oil of turpentine were prepared by exposing a mixture of oil, water and emulsifying agent in a suitable exposure chamber. The best results were obtained by using hard soap, followed by polyethylene glycol 400 monostearate, polysorbate 80, acacia and sodium lauryl sulphate. Tragacanth was the least effective emulsifying agent, apparently because it acts by increasing the viscosity of emulsions and this property is affected by ultrasonic waves. The maximum exposure time employed in these experiments was 30 minutes, and the size of the oil globules appeared to decrease with increase in exposure time up to this limit. G.B.

Ophthalmic Solutions, An Evaluation of Chemical Preservatives for. C. A. Lawrence. (*J. Amer. pharm. Ass., Sci. Ed.*, 1955, **44**, 457.) Several chemical preservatives were tested for bactericidal activity against 26 strains of *Pseudomonas æruginosa* and 4 species of *Proteus*. The chemicals were allowed to remain in contact with the organisms for definite periods of time from 30 minutes to 6 days, after which a loopful of solution was transferred to a suitable culture medium and tested for sterility. For thiomersalate and phenylmercuric nitrate, Brewers' thioglycollate medium was used to inactivate the antiseptic, while benzalkonium chloride was inactivated by using beef extract broth containing 0·1 per cent. of Asolectin and 0·7 per cent. of Tween 20. All substances tested were more active against *Proteus* than against *Pseudomonas* cultures, and benzalkonium chloride was the most effective agent studied. Phenylmercuric nitrate was more active than thiomersalate against *Pseudomonas æruginosa*, and phenylethyl alcohol appeared to be relatively inactive against these organisms. Similar results were obtained by testing the substances in distilled water and in solutions of ophthalmic drugs such as atropine sulphate, homatropine hydrobromide, pilocarpine nitrate and penicillin (potassium salt). G. B.

PHARMACOLOGY AND THERAPEUTICS

Antibiotics and Aluminium Hydroxide, Incompatibility of. A. Albert and C. Rees. (*Brit. med. J.*, 1955, **2**, 1027.) The administration of aluminium hydroxide with the tetracycline group of antibiotics to counteract the digestive upsets which often follow their oral use is condemned as an undesirable practice. The authors carried out the following experiment: aluminium hydroxide gel 8 ml.

was added to chlortetracycline hydrochloride 0·25 g. in water 250 ml. From the pH (6·48) and from the data yielded by potentiometric titration in the presence of known concentrations of aluminium cations they calculated that all the drug was firmly bound to the aluminium hydroxide, and it is unlikely that it would be liberated to any extent during the passage of the aluminium complex along the intestinal tract. The abolition of digestive upset is therefore explained by the fact that the drug is no longer present. The other tetracyclines behave similarly and it is suggested that milk should replace aluminium preparations as a protective agent for the gastro-intestinal tract when these antibiotics are administered. S. L. W.

Chlorpromazine Hydrochloride in the Treatment of Tetanus. A. C. E. Cole and D. H. H. Robertson. (*Lancet*, 1955, **269**, 1063.) In the belief that chlorpromazine hydrochloride is an antagonist to some central convulsant drugs and that it potentiates the action of hypnotics, it was given in conjunction with phenobarbitone or chloral hydrate to six African patients with tetanus. The drug was given in doses of 50 mg. either intramuscularly, diluted to 10 ml., or intravenously, diluted to 20 ml. The tetanic spasm was relieved dramatically; the abdominal and back muscles were moderately or completely relaxed, convulsive seizures were inhibited and a lazy sleepiness supervened. The simultaneous injection of 3 grains of soluble phenobarbitone prolonged the effect for up to 12 hours. For children, chloral hydrate was given orally instead of the phenobarbitone. Insufficient cases have been treated to show whether there is any effect on mortality. Oral treatment with 10 or 25 mg. of chlorpromazine hydrochloride was less effective but was useful when the patients were recovering. H. T. B.

Chlorpromazine, Reserpine, and Isoniazid in Mental Disorder. J. K. Hewat, P. W. W. Leach and R. W. Simpson. (*Brit. med. J.*, 1955, **2**, 1119.) This is the report of a pilot trial to assess the toxic effects of these three drugs used in combination in psychiatric conditions. Sixteen patients with chronic psychoses were treated for 3 weeks by the oral administration of a compound tablet containing chlorpromazine 25 mg., reserpine 1 mg., and isoniazid 50 mg. Beginning with one tablet, the dose was increased every day until 4 tablets daily were being given. The outstanding result was the unexpectedly high incidence of extrapyramidal signs. Parkinsonism occurred in 6 patients, tremor in 4, drowsiness in 11, insomnia in 1, dizziness in 2 and headache in 1. Other side-effects included a fall in blood pressure, nasal congestion, dryness of mouth, pallor, flushing, increase in weight, pains in trunk and limbs, malaise and weakness, and shivering. A further trial on another series of 16 patients was carried out, using half the dosage—namely, chlorpromazine 50 mg., reserpine 2 mg., and isoniazid 100 mg., daily for 4 weeks. The side-effects were markedly reduced. Parkinsonism was entirely absent, tremor occurred in 1 patient, drowsiness in 3, and giddiness in 2. The hypotensive and bradycardic trends were similar to those in the first trial. In both trials all side-effects cleared rapidly when treatment was stopped. These preliminary observations, over a short period on a small number of patients, did suggest that the combination of the drugs had a definite effect on the mental state. After the first trial 7 were worse, 5 unchanged, and 4 were better. After the second trial 2 were worse, 3 unchanged, and 9 were better (1 uncompleted). Where the effect was beneficial the trend was towards a quieter, more co-operative and more relaxed patient. Although Parkinsonism is known to occur with chlorpromazine and reserpine when used

singly in large doses its occurrence with small doses in combination was unexpected and suggests that these two drugs may have a potentiating action. This action is perhaps not entirely undesirable since it may have therapeutic significance. The authors conclude that these preliminary trials did not reveal any contraindication to proceeding with large-scale trials they are planning to undertake. S. L. W.

Cortisone, Influence on Connective Tissue, Epithelial Relations in Wound Healing, Hair Regeneration and the Pathogenesis of Experimental Skin Cancers. T. Gillman, J. Penn, D. Bronks and M. Roux. (*Nature, Lond.*, 1955, **176**, 932.) Cortisone diminished, through suppression of the usual connective tissue responses, wound healing in rabbits and hair regeneration after plucking, and tumour development after painting the skin with methylcholanthrene, in mice. In the case of tumour development, neoplasia within the epidermis itself were not eliminated, but the incidence of papillomata and the subsequent neoplasia in such benign tumours was decreased after cortisone. Histochemical findings indicate that cortisone induces its effects by acting on ribose nucleic acid and/or mucopolysaccharide metabolism of the dermis, thereby influencing epidermal responses to various stimuli. G. P.

Cortisone in Ulcerative Colitis. S. C. Truelove and L. J. Witts. (*Brit. med. J.*, 1955, **2**, 1041.) A therapeutic trial of cortisone in non-specific ulcerative colitis was carried out on a series of patients in 5 hospital regions. Of the 210 patients concerned 109 were treated with cortisone, the usual dose being up to 100 mg. a day for 6 weeks, and 101 received an inert preparation. At every stage of severity of the illness, and in both first attacks and relapses, the cortisone-treated patients did better than the control patients. Cortisone was particularly beneficial in first attacks. Patients treated with cortisone were more likely to suffer from pyogenic complications and when using this treatment it is probably wise to employ penicillin or sulphonamides in addition. Follow-up information is available for an average period of 18 months for 205 of the patients. Nine months after the trial period patients treated with cortisone in the first attack preserved a clear advantage over the corresponding control group. On the other hand, relapse cases treated with cortisone had lost the initial advantage they showed at the end of the trial period. At the end of the follow-up period, essentially the same pattern existed as at nine months, but with a slight worsening of the general picture. About one-fifth of the original group had been treated by ileostomy by the end of the study; of these 44 patients, 14 were dead at the end of the study. There would seem to be good grounds for advising that early cases of ulcerative colitis should promptly be brought under treatment with cortisone, which should, if necessary, be given in considerably higher dosage than used in this trial. Where treatment is successful, as it is likely to be in a substantial proportion of cases, the patients should be kept under careful supervision so that treatment can be promptly resumed if symptoms recur. Once irreversible damage has been done to the colon and the patient has persistent troublesome symptoms, it is wisest for him to submit to ileostomy, which is nowadays usually combined with colectomy. While it is true that cortisone greatly increases the chances of remission or improvement in all grades of chronic ulcerative colitis, nevertheless it is not a specific, and its effect is far from permanent, especially in the established disease. S. L. W.

***p*-(Di-2-chloroethylamino)-phenylbutyric Acid (CB 1348) in Malignant Lymphoma.** D. A. G. Galton, L. G. Israels, J. D. N. Nabarro and M. Till.

(*Brit. med. J.*, 1955, **2**, 1172.) This compound is a water-soluble aromatic nitrogen mustard which has been shown to be a powerful inhibitor of the transplanted Walker rat tumour. Ninety-three patients suffering from advanced carcinoma and from lymphomas have been treated with the compound since September 1952. This report concerns 62 cases of malignant lymphoma; these include 23 of Hodgkin's disease, 20 of lymphocytic lymphoma, 11 of reticulum cell sarcoma, 6 of follicular lymphoma and 1 each of generalised exfoliative erythrodermia and mycosis fungoides. Administration was usually by mouth, the dose ranging from 2 to 20 mg. a day (0·03 to 0·34 mg./kg.); in most cases it was either 0·1 or 0·2 mg./kg. daily. A course of treatment usually lasted 3 to 6 weeks, but the drug was given daily for 8 to 16 weeks on 13 occasions and for 6 to 12 months on 3. Eighteen patients had more than one course of treatment; 15 were given 2 courses at intervals of 3 to 27 months; 2 had 3 courses; and 1 had 6. Treatment was stopped when satisfactory improvement had been obtained. If there was no response treatment was usually continued for 6 weeks before concluding that the patient was resistant to the drug. In a few cases the drug was given by intravenous injection, the sodium salt being freshly made up in isotonic sodium bicarbonate. Single doses varied from 10 to 20 mg.; in one case single doses of 70 mg. were given. The injections were well tolerated and did not damage the veins or cause vomiting. Striking remissions were obtained in 4 cases of Hodgkin's disease, 7 of lymphocytic lymphoma, 4 of chronic lymphocytic leukæmia, and 5 of follicular lymphoma. The drug is relatively free from gastro-intestinal side-effects and has proved less damaging to haemopoietic tissue than cytotoxic agents hitherto available for the treatment of malignant lymphoma. It is safer than tretamine, especially when repeated courses are required. The dosage of CB 1348 likely to cause bone marrow damage almost always lies well outside the therapeutic range, at any rate for first courses. S. L. W.

Ecolid: A New Hypotensive Agent. R. D. H. Maxwell and T. J. G. Howie. (*Brit. med. J.*, 1955, **2**, 1189.) Ecolid is 4:5:6:7-tetrachloro-2-(dimethylaminoethyl)-*iso*indoline dimethochloride. It is a ganglion-blocking agent which has been shown in animal experiments to be several times as active by parenteral dosage as hexamethonium and twice as active as pentolinium. In oral dosage its activity is the same as pentolinium but the duration of action is appreciably longer. Vagal activity is affected less than sympathetic. Twelve patients suffering from severe hypertension were treated with ecolid. It was determined that the initial dose should not exceed 25 mg. and treatment consisted of 25 to 200 mg. administered before breakfast with a dose also during the evening if required. The treatment has been used in this series of patients over 4 months and it has been found possible to lower the blood pressure to a satisfactory level in every case. The severity of side effects depended to some extent upon the dosage used. Mydriasis was a constant finding and blurring of vision commonly occurred during initial treatment but was less severe with maintenance dosage. Precautions were necessary to overcome development of constipation and in 3 cases treatment had to be stopped owing to nausea, vomiting, and obdurate constipation. A combination of reserpine with ecolid was used in the maintenance treatment of 6 of the patients, reserpine, 2 mg. by mouth, being given in the evening. Reduction in the maintenance dose of ecolid was found possible and side-effects were fewer. During the period of observation tolerance to ecolid has not developed and in some cases reduction of dosage has been possible. The response was good in 8 cases and fair in 1, the drug being stopped in the remaining 3 owing to side-effects. S. L. W.

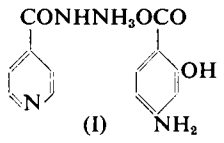
Noradrenaline in the Treatment of Acute Cor Pulmonale. J. de Swiet. (*Brit. med. J.*, 1955, **2**, 1253.) The use of (−)-noradrenaline in the treatment of the shock and hypotensive state following acute myocardial infarction suggested its use in combatting the profoundedly hypotensive condition resulting from massive pulmonary embolism. A case is described in which pulmonary embolism occurred after partial gastrectomy. Treatment with aminophylline, heparin and pethidine was started immediately, and a course of ethyl biscoumacetate was also begun. After an hour, the blood pressure still being extremely low, an intravenous infusion of 4 ml. of Levophed, containing 4 mg. of (−)-noradrenaline, in a litre of 0·2 N saline was begun at a rate of 30 drops/minute, the rate being varied from 25 to 35 drops/minute according to the blood pressure. A further 4 ml. of Levophed was added after 1 hour, and thereafter 4 ml. half hourly for 6 additions, at which time the drip was delivering about 45 μg./minute of noradrenaline. For the following 4 days, the drip contained 64 ml. of noradrenaline, delivering 90 μg./minute. Subsequently the patient twice collapsed but recovered when the noradrenaline dosage was increased to 150 μg./minute and thereafter the concentration was gradually reduced to zero. The total dosage was 798 mg. during 11 days. Profuse sweating was the only evidence of any toxic effect. H. T. B.

Noradrenaline, Skin Necrosis Following Intravenous. J. Humphreys, J. H. Johnston and J. C. Richardson. (*Brit. med. J.*, 1955, 2, 1250.) Extreme local vasoconstriction resulting in gangrene of the skin and subcutaneous tissues occurred 5 times in 3 cases following the administration of noradrenaline into a superficial vein. The patients had respectively undergone a subtotal colectomy for ulcerative colitis, panhysterectomy and abdomino-perineal resection for carcinoma, and urethral dilatation for stricture. In the first case, 2 mg. of noradrenaline in 0·5 l. of 5 per cent. dextrose solution was given into the left internal saphenous vein in the ankle and after 150 ml. had been given a mottled blue and white appearance of the leg was noticed. The infusion was stopped and given into the other ankle but the same effect was immediately produced. Necrosis followed in both legs. The second patient received a total of 450 mg. of noradrenaline in 7 different veins over about 3 weeks and skin necrosis occurred over 2 of the 3 veins where a tied-in cannula was used but not where the 4 percutaneous infusions were given. In the third patient signs of tissue necrosis appeared 46 hours after starting a drip infusion into an internal saphenous vein. The authors consider that the concentration of noradrenaline in the infusion is not significant but that the important factor is the concentration of the drug in the vein lumen. If given through a needle inserted percutaneously into a large vein it is rapidly diluted by the circulating blood, whereas with a tied-in cannula the recipient vein contains only the solution until it is joined by a large tributary. If the veins are collapsed and a cut-down is necessary, it is suggested that the drug be given through polythene tube passed far enough proximally to enable its tip to lie in a vein considerably greater in diameter than its own. [*Abstractor's Note.* M. T. Harrison (*Brit. med. J.*, 1955, **2**, 1502) reports two cases of necrosis in spite of the passage of a polythene cannula a long distance up the long saphenous vein.] If the skin overlying a vein receiving the drug shows colour changes, the administration must be stopped at once. Early injections of procaine and papaverine into the vein may possibly relieve the vasoconstriction. H. T. B.

Organic Phosphates, Pharmacological Effects of. R. E. Bagdon and K. P. Dubois. (*Arch. int. Pharmacodyn.*, 1955, **103**, 192.) The pharmacological actions of *p*-nitro-*m*-chlorophenyl dimethyl thionophosphate (Chlorthion),

(S-[1 : 2-dicarbethoxyethyl]*OO*-dimethyl dithionophosphate (malathion) and tetrapropyl dithionopyrophosphate have been studied and compared with the highly active organic phosphate 2-mercaptoethyl thionophosphate (systox). Intravenous injections into normal dogs caused increased urination, diarrhœa, copious salivation and deepened respirations. High doses showed the characteristic effects of poisoning by anticholinesterase agents. In anæsthetised dogs the compounds caused a fall in blood pressure, bradycardia and potentiated the actions of acetylcholine. The dose of systox causing death in dogs was 100 to 240 times less than the other compounds. The isolated rabbit heart was resistant to chlorthion, malathion, tetrapropyl dithionopyrophosphate and systox. Atropine in the perfusion fluid gave no protection. Tetrapropyl dithionopyrophosphate and systox caused a rise in tone of the isolated rabbit intestine and high doses spastic contractions. The peristaltic response was blocked by atropine or nicotine. Chlorthion and malathion stimulated the intestine, but in high doses caused a depression of tone. G. F. S.

PAS Salt of Isoniazid: Clinical Trial in Pulmonary Tuberculosis. W. J. Clegg. (*Brit. med. J.*, 1955, **2**, 1004.) The drug employed in this trial, called GEWO 339, is an additive compound between PAS and isoniazid to which the formula (I) is attributed. The substance is said to inhibit the growth of ordinary strains of tubercle bacilli at a concentration of 0·1 μg./ml. of medium. It is also claimed that strains resistant to isoniazid and PAS either alone or in combination, though not as sensitive as normal strains to GEWO 339, were still sensitive at therapeutic levels. Strains which grow normally on media containing 100 μg. of isoniazid and also media containing 100 μg. of PAS were inhibited by 5 μg./ml. of the new compound. For the purposes of the trial 17 patients were treated, all of whom were suffering from bilateral chronic pulmonary tuberculosis with cavitation. Each patient received a daily dose of 600 mg. of the compound in three doses of 200 mg. given as 100 mg. tablets, the treatment continuing for a period of 12 weeks. The most striking change following the treatment was the remarkable lowering of the positivity of the sputum. In only 1 case was there no significant alteration in the character of the sputum; in 10 cases there was a marked drop in both the volume and the bacillary content of the 24-hour samples, and in 6 cases sputum conversion occurred, none of whom, in spite of long periods of antibacterial treatment, had previously had sputum conversion. In only one of the cases did partial resistance develop during treatment. The drug was well tolerated in all cases. Most of the patients had previously taken large doses of PAS, isoniazid, and streptomycin, and the great majority expressed their appreciation of the ease with which the new compound could be taken in comparison with the nausea associated with large doses of PAS. Since the drug proved active *in vivo* and drug resistance did not develop quickly, the author states that it is hoped to organise a full-scale trial. S. L. W.



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Phenoxymethylpenicillin; Comparison with Benzylpenicillin on Oral Administration. W. W. Wright, A. Kirshbaum, B. Arret, L. E. Putnam and H. Welch. (*Antibiotic Med.*, 1955, **1**, 490.) This paper discusses the potency of phenoxymethylpenicillin (Penicillin V) when tested by various methods, and the serum and urine concentrations obtained following oral administration. When tested against numerous strains of *Micrococcus pyogenes* var. *aureus* it was found superior to benzylpenicillin against both penicillin-sensitive and

penicillin-resistant strains. In the latter cases its superiority was not sufficiently great to say that a significant number of benzylpenicillin-resistant strains are sensitive to phenoxymethylpenicillin. Thus, in spite of the greater over-all activity of the latter no clinical advantage would be expected from its use if it were present in the blood in the same amount as benzylpenicillin. Controlled experiments on 30 normal subjects showed that phenoxymethylpenicillin does produce higher blood concentrations than benzylpenicillin. When given orally, this is probably due to its greater stability in an acid environment. This is reflected also in the urinary excretion of active phenoxymethylpenicillin in quantities double those obtained with benzylpenicillin. In the light of these findings the authors consider that the use of phenoxymethylpenicllin may be advantageous in oral penicillin therapy. S. L. W.

Prednisone and Prednisolone in Rheumatoid Arthritis. F. D. Hart, C. J. M. Clark and J. R. Golding. (*Lancet*, 1955, **269**, 998.) Ten rheumatoid patients were transferred from cortisone to either prednisone or prednisolone (15 to 30 mg. daily) and back to cortisone, and 4 from prednisolone direct to cortisone. Assessment was by the patients' own estimation of pain and stiffness, by finger swelling, tenderness over joints, erythrocyte-sedimentation rate, simple function tests, and power of grip. The length of treatment with prednisone or prednisolone (the two substances appear identical in action) varied from 4 days to 10 weeks. The results of this short-term investigation showed that either of these drugs is a more effective agent than cortisone in four or five times the dose in relieving the symptoms and signs of rheumatoid arthritis. In no single detail in any of the 14 cases did cortisone give a better assessment figure. Of the 14 patients, 9 preferred prednisone or prednisolone to cortisone, 5 were indifferent, and none preferred cortisone. Over-all improvement took place in 10 of the 14 cases on transferring from cortisone to prednisone, whereas 8 deteriorated somewhat on returning to cortisone. No toxic effects of the new products were observed. S. L. W.

Prednisone, Clinical and Metabolic Effects of. J. D. N. Nabarro, J. S. Stewart and G. Walker. (*Lancet*, 1955, **269**, 993.) The clinical effects of prednisone, in a dose of 30 to 40 mg. daily, were observed in 5 cases of lymphatic leukæmia, 2 cases of lymphoma and 1 case of Henoch-Schönlein syndrome. In addition, prednisone (30 mg. daily) was given to a normal subject during a balance study, and varying amounts were given to 2 adrenalectomised women to study the effect on steroid excretion. Seven of the patients had been receiving cortisone in large doses (100 to 150 mg. daily) for periods up to 12 months, and in 6 of the patients this had produced a dramatic improvement in the general condition and well-being. When prednisone was substituted for cortisone the improvement was maintained. An eighth patient, in whom steroid therapy was initiated with prednisone, also showed an excellent response to treatment. Of the 7 patients who had been receiving cortisone 4 had had œdema, 1 severe dyspepsia and osteoporosis with vertebral collapse, 1 had steroid diabetes, 1 was euphoric and 1 had developed a moon-face. Transfer to prednisone abolished the œdema and improved salt tolerance but was without effect on the other complications; 2 patients developed diabetes while on prednisone. It would appear that prednisone is about five times more active than cortisone in maintaining the hæmoglobin level and reducing the size of lymphomatous deposits. This therapeutic ratio is similar to that observed in rheumatoid arthritis and asthma. The sodium-retaining activity of prednisone is not increased in parallel with the therapeutic activity and most patients are able to take prednisone (30 to 40 mg. daily) with a normal sodium intake. Prednisone causes adrenal sup-

pression and patients receiving long-term treatment will be in a state of adrenal deficiency if the steroid is abruptly withdrawn. The fact that prednisone can be given without restriction of salt intake and with little risk of œdema developing may encourage prolonged administration in high dosage, but the other and more serious complications of steroid therapy are just as easily produced and it is essential to keep the dose as low as possible. S. L. W.

Radioactive Iodine in the Treatment of Thyrotoxicosis. G. W. Blomfield, J. C. Jones, A. G. Macgregor, H. Miller, E. J. Wayne and R. S. Weetch. (*Brit. med. J.*, 1955, **2**, 1223.) The authors give a detailed analysis of the results obtained with radioactive iodine in 106 female and 34 male cases of thyrotoxicosis followed up for at least a year. Most of the patients received a single dose of ^{131}I calculated to deliver to the gland a dose of 6000 to 8000 rads (1 rad = 100 ergs/g. of gland tissue), the calculation being based on the effect of a preliminary tracer dose. Patients needing rapid control of the thyrotoxic state were treated with an antithyroid drug before treatment with ^{131}I. 36 patients received more than one dose, one of them having a resistant post-operative recurrence which was treated with 5 doses over a period of 2 years. Results were assessed on clinical grounds. At the time of assessment 118 patients were euthyroid and 17 were hypothyroid, while 4 were still thyrotoxic although one felt so well that further treatment was refused. The average time for achieving euthyroidism in single-dose cures was about 4½ months. Of the hypothyroid cases, 9 needed only 0·1 mg. of L-thyroxine sodium per day to maintain thyroid balance. Two patients unwittingly received treatment while pregnant but both pregnancies proceeded normally to full term and the babies have developed normally. The authors conclude that the risk of radiation-induced neoplasms in the thyroid gland is slight, although the final answer cannot be known for another decade. As a precaution they suggest that, in general, the treatment should be given only to those whose life expectation does not exceed 20 years. A few patients complained of transient aching over the front of the neck for a few days after the dose. Two developed urticaria which needed prolonged antihistamine therapy before it abated. Thrombocytopænia occurred temporarily in one patient but may not have been due to the treatment. 15 patients complained of rheumatic symptoms, either articular or non-articular, but this also may not have been due to the isotope. The main problem in treatment is the determination of dosage. Scintillation counting techniques are of value in determining the size of the gland but there is a discrepancy between the actual uptake of ^{131}I and the uptake indicated by the tracer dose. H. T. B.

Rauwolfia in Hypertension. J. H. Moyer, E. Dennis and R. Ford. (*Arch. intern. Med.*, 1955, **96**, 530.) This report is a study of rauwolfia in the treatment of hypertension, its object being to compare the clinical results obtained with single pure alkaloids of rauwolfia (reserpine and rescinnamine) with those obtained with preparations containing multiple active alkaloids. The latter included whole root, Alseroxylon (a standardised alkaloidal extract containing reserpine, rescinnamine and other hypotensively active alkaloids not yet characterised) and Roxinil (an extract containing multiple alkaloids of both reserpine-like and serpentine-like material). A total of 346 cases of hypertensive vascular disease was treated. Most of the patients were treated as outpatients and were observed for a control period of from 1 to 3 months before treatment. The criterion for inclusion in the study was an average control blood pressure greater than 150/100. All patients received placebos during the control period. If the systolic or diastolic pressure fell below this level under placebo therapy the patient was discarded from the study. The criteria for responsiveness to

drug therapy was a fall of at least 20 mm. Hg. in the average upright mean blood pressure, or a fall below 150/100 mm. Hg. which was considered the normotensive level. The patients were divided into 5 groups according to the drug they received. The post-treatment blood pressure in each case was taken as an average of all recordings made after the first 6 weeks of treatment with one of the preparations. The study showed that there was no significant difference, quantitatively or qualitatively, in the hypotensive action of the 5 products. The hypotensive activity of 1 mg. of reserpine is estimated to be about equal to that of 250 mg. of crude root or 4 mg. of Alseroxylon. The side-effects of the 5 products were qualitatively similar but quantitatively there were minor differences. Reserpine produces more weakness, fatigue and sedation than either rescinnamine or extracts containing multiple alkaloids. Reserpine produced mental depression in a number of cases and this was not observed with rescinnamine and was much less frequent with Alseroxylon or crude root. All the preparations tested were bradycrotic but rescinnamine appeared somewhat less so than the others. All the preparations had a slow onset of action but reserpine appears somewhat more rapid than the others. S. L. W.

Reserpine and Rauwolfia in the Treatment of Psychoneuroses. A. Folkson and A. R. May. (*Brit. med. J.*, 1955, **2**, 1121.) In this investigation the effects of reserpine and rauwolfia were studied in 75 psychoneurotic patients. The patients were assessed in two separate groups. In group A (consisting of 30 patients) each patient received the active drug or a placebo in alternate courses lasting a month each. In group B (45 patients) the patients acted as their own controls. Most of the patients were out-patients and all were treated by the oral route. Sixty-seven patients received reserpine in a dose of 0·25 mg. three times daily initially rising to 0·5 mg. three times daily where this could be tolerated. Seventeen patients received rauwolfia in a dose of 2 mg. twice daily, and of these 9 patients subsequently received reserpine. The duration of treatment in both groups varied between 2 and 6 months. The investigation failed to confirm the results claimed in a number of psychiatric disorders. In group A no improvement occurred with either drug. In group B 6 patients benefited from reserpine of whom 3 were hypertensive. The authors suggest that these results indicate a possible discrepancy in the methods of assessment and the need for adequate control in such investigations. Side-effects in this series were infrequent and slight in nature. S. L. W.

Vitamin K_1 Intravenously, Effect on the Action of Phenindione. P. Dawson. (*Brit. med. J.*, 1955, **2**, 1427.) This paper records the results of tests performed on 24 volunteers receiving phenindione who were given intravenous injections of a stable emulsion containing 20 mg. of vitamin K_1/ml. Doses of 10 to 20 mg. of vitamin K_1, thus administered, were found to return the prothrombin activity to 100 per cent. within 24 hours in subjects continuing to take phenindione. These doses were also found effective within 24 hours in correcting a moderate deficiency of prothrombin itself. A dose of 5 mg. caused a rise of between 50 and 100 per cent. prothrombin activity within the same period. In more than half the experiments an appreciable rise of prothrombin activity occurred within 3 hours. In the treatment of hæmorrhage due to phenindione an intravenous dose of 10–20 mg. is likely to be effective. If vitamin K_1 is given merely to raise a dangerously low prothrombin activity to within therapeutic range the evidence suggests that even 5 mg. may be too large a dose if anticoagulant resistance in the subsequent days, with its danger of further thrombosis, is to be avoided. No toxic effects were observed during 40 intravenous injections of the vitamin K_1 emulsion. S. L. W.

BACTERIOLOGY AND CLINICAL TESTS

Influenza Virus Vaccines: Effects of Saline and Oil Adjuvants. (Second Progress Report by the Medical Research Council's Committee on Clinical Trials of Influenza Vaccine.) (*Brit. med. J.*, 1955, **2**, 1229.) Tests were carried out on 399 volunteers of the reactions and serological responses to three types of influenza vaccines—A: a water-in-oil emulsion of mouse-adapted virus, in doses of 0·25 ml. containing 2000 hæmagglutinating units; B: as A, but using egg-adapted virus; and C: mouse-adapted virus containing 20,000 hæmagglutinating units per dose of 1 ml., in saline to which 10 mg. of aluminium phosphate had been added. Each vaccine also contained 0·01 per cent. of thiomersal in the aqueous phase. A and B were given intramuscularly and C subcutaneously. There was no significant difference in the incidence of general reactions such as pyrexia, malaise, lassitude and nausea; they occurred in relatively few instances. Erythema and swelling, either alone or together, were found chiefly in volunteers receiving vaccine C. Induration at the site of inoculation occurred in 43 volunteers in the C group, 19 in the B group and 13 in the A group. In some cases it persisted, the figures at 6 months being 8, 2 and 1 and at 1 year 4, 2 and 0. In comparing the difference in the incidences of induration account must be taken of the greater difficulty in detecting it with A and B vaccines, which were given intramuscularly. Two volunteers, one given vaccine A and one given vaccine B, had unusually persistent and extensive local reactions, suggesting abscess formation although neither led to liquefaction or cyst formation. The peak in antibody titre was obtained at 2 weeks with vaccines C and 3 months with A and B, and the responses to A and B were greater and more prolonged than the response to C. After one year the mean titre in the C group was about 5 times the initial level, in the B group 7 times and in the A group 11 times. It is not certain that the differences in the results obtained with the A and B vaccines are significant since factors such as small antigenic differences and differences in the avidity for antibody may be concerned. H. T. B.

Organic Mercury Compounds, Bacteriostatic and Bactericidal Effect of. O. G. Clausen (*Medd. Norsk. Farm. Sels.*, 1955, **17**, 313.) In tests for the bacteriostatic effect of thiomersalate and phenylmercuric acetate and nitrate, 13 ærobic organisms and 1 anærobe (*Clostridium welchii*) were used. Three 'natural inocula' were also used in the tests, suspension of normal fæces, sputum suspension and dust suspension. These were chosen as representing microbial contamination more severe than is likely to be encountered during the preparation of solutions for injection and eye drops. Thiomersal was effective in the highest dilution, 1 in 50,000 being effective as a bacteriostatic against all the organisms and materials studied. The corresponding dilution for phenylmercuric acetate was 1 in 20,000, and for the nitrate 1 in 25,000. The organisms most resistant to thiomersalate were *C. welchii* and *Pseudomonas æruginosa*, those most resistant to phenylmercuric acetate were *Ps. æruginosa*, *C. welchii*, *Klebsiella pneumoniæ* and *Escherichia coli*, and those most resistant to the nitrate were *C. welchii*, *Ps. æruginosa and K. pneumoniæ*. Bactericidal tests were performed by allowing the antiseptics to act for 10 minutes at 37° C., and then inoculating a sample into thioglycollate medium which served as an inactivating agent. Owing to the comparatively slow bactericidal action of mercurial antiseptics, phenol coefficients could not be accurately determined, but using *Micrococcus pyogenes* var. *aureus* as test organism the phenol coefficient of thiomersalate was less than 10, and that of the phenylmercuric compounds was less than 25, whereas using *E. coli* the coefficients were less than 12·5 and less than 31·25. G. B.