ABSTRACTS OF PAPERS PUBLISHED IN OTHER JOURNALS

CHEMISTRY

ANALYTICAL

Alkali Metals in the Presence of Calcium and Magnesium, Determination of. O. Samuelson and E. Sjöström. (*Analyt. Chem.*, 1954, **26**, 1908.) A method is given for the determination of potassium, sodium and lithium in the presence of calcium and magnesium. Experiments showed that calcium and magnesium could be taken up in a column containing an anion exchanger in ethylenediaminetetra-acetic acid form, the uptake being better from an ethanol-water mixture than from an aqueous solution. The ethylenediaminetetra-acetic acid form of the resin was prepared by passing a solution of disodium ethylenediaminetetra-acetate over a resin in the acetate form. When the free-base form in the mixed resin was substituted for the acetate form, not only potassium but also sodium and lithium could be removed by washing with a moderate amount of 60 per cent. ethanol. After the removal of the bivalent ions, the alkali metals in the effluent from the first column were passed directly through a second column containing the free-base form of an anion exchanger of the strongly basic type; the resulting alkali hydroxides were titrated with standard acid. R. E. S.

Bismuth, Complexometric Titration of. K. L. Cheng. (*Analyt. Chem.*, 1954, **26**, 1977.) A method is described for the direct titration of bismuth with disodium ethylenediaminetetra-acetate using potassium iodide as the indicator. The titration is carried out between *p*H 1·5 and 2·0 in which range few metals form complexes of sufficient strength to cause interference. Below *p*H 1 the end-point was not sharp while it was also impossible to titrate bismuth at a *p*H higher than 2·5 owing to the precipitation of bismuth hydroxide. In the direct titration procedure the amount of potassium iodide added was such that bismuth was not precipitated out but formed an intense yellow colour; further iodide was added just before the end-point which was from yellow to colourless. Details are also given for a back-titration procedure with standard bismuth solution. The following metals interfered: thallium, cerium, iron, titanium, zirconium, silver, mercury, molybdenum and vanadium. R. E. S.

Bismuth, Titration of, with Ethylenediaminetetra-acetic Acid. J. S. Fritz. (*Analyt. Chem.*, 1954, **26**, 1978.) A method is given in which bismuth is titrated directly with disodium ethylenediaminetetra-acetate, forming a stable, soluble complex; excess thiourea is added to form a weak complex with bismuth and thus prevent any precipitation before or during the titration. The end-point is given by the disappearance of the last yellow colour due to the complex. Experiments showed that a low thiourea concentration (0·5 to 1·0 g. thiourea per 50 ml. of solution) gave a sharp end-point in the *p*H range 1·5 to 2·0; concentrations of thiourea above and below this range gave end-points which were less sharp. A study of interfering metals is reported; lead did not interfere, even with a lead-bismuth ratio of 30:1, and in many instances anions could be used as masking agents. Samples containing highly coloured ions could be titrated using the colour of a blank as the end-point, although for very highly coloured solutions a photometric titration would be necessary. R. E. S.

Cortisone, Hydrocortisone, Aldosterone and Related Steroids, Colorimetric Reaction for. I. Clark. (*Nature, Lond.*, 1955, **175**, 123.) Diphenylamine in the presence of acetic and sulphuric acids reacts with steroid compounds having keto and hydroxyl groups to give coloured compounds. The colour and the absorption curves of the compounds formed depend on the positions of these groupings. Different absorption maxima with cortisone and hydrocortisone enable the determination of both substances in a mixture. G. F. S.

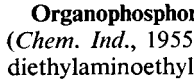
Digitalis Glycosides, Determination of the Purity of. J. E. Murphy. (*J. Amer. pharm. Ass., Sci. Ed.*, 1954, **43**, 659.) 1 ml. of a 0·1 per cent. solution of the glycoside under test in chloroform-methanol solution is evaporated to dryness on a water bath. 10 ml. of a reagent consisting of equal volumes of propylene glycol and hydrochloric acid at 20° C. is added and the mixture stirred and kept at 20° C. for 30 minutes. The fluorescence is measured with the aid of a photofluorimeter, and the content of fluorescing substances, calculated as gitoxin, is determined by comparison with the fluorescence of a gitoxin standard, similarly treated. When the content of fluorescing impurities exceeds about 8 per cent., there may be non-linearity of instrument response, and the result should be calculated with the aid of a standard curve. Solutions for injection may be examined after evaporating a sample and proceeding as above, Tablets are submitted to a preliminary extraction procedure, although in some cases stirring the powdered tablets with chloroform-methanol and pipetting after allowing the sediment to settle, is satisfactory. Most of the common excipients used in tablets do not affect the test. Equimolecular concentrations of gitoxin, gitoxigenin, *D. purpurea* glycoside B and lanatoside B give the same fluorescence. At least 2 other (unknown) glycosides are sometimes found in small amounts in digoxin. G. B.

Tyrothrycin Antibiotics, Influence of Quaternary Ammonium Compounds in the Assay of. L. L. Nisonger. (*J. Amer. pharm. Ass., Sci. Ed.*, 1954, **43**, 716.) Preparations of methylol gramicidin containing cetylpyridinium chloride as a solubilising agent were assayed by a turbidimetric serial dilution method against a species of *Streptococcus*. High values were obtained for the bacteriostatic power of the antibiotic, owing to the presence of the cationic surface-active agent. Attempts to separate the components, or to inactivate the cetylpyridinium chloride were unsuccessful. A straight-line relationship was shown to exist between the ratio of apparent to real potency and the proportion of cetylpyridinium chloride to methylol gramicidin. An equation was established with the aid of which microbiological assay results may be accurately interpreted, provided that the concentration of cetylpyridinium chloride is accurately known. G. B.

ORGANIC CHEMISTRY

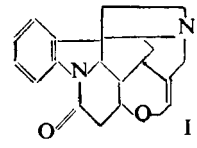
Fungicides, *s*-Triazine Derivatives, a New Class of. C. N. Wolf, P. H. Schuldt and M. M. Baldwin. (*Science*, 1955, **121**, 61.) A study of a series of substituted *s*-triazines has shown that compounds from the class of 2 : 4-dichloro-*s*-triazines, having arylamino or aryloxy groups in the 6- position, have a high fungitoxic activity. The compounds were tested against *Alternaria oleracea* and *Sclerotinia fructicola* by a slide germination method. In field trials the compound 2:4-dichloro-6-(*o*-chloroanilino)-*s*-triazine has shown promise of effective control of apple scab, celery early blight, muskmelon leaf spot, onion-foliage diseases, leaf diseases of ornamentals, potato late blight, tomato anthracnose, dollar spot and diseases of the turf caused by Helminthosporium. G. F. S.

Organophosphorus Pesticides, New Group of. R. Ghosh and J. F. Newman. (*Chem. Ind.*, 1955, 118.) The organophosphorus compound *OO'*-diethyl-*S*-β-diethylaminoethyl phosphorothiolate I is a colourless liquid, b.pt. 97° C./0·2 mm., which formed well defined crystalline salts with acids. I and its salts are highly effective and persistent systemic toxicants to various species of red spider mites. In laboratory tests as a direct contact spray on the glasshouse red spider mite on its food plant, a concentration of less than 2 p.p.m. produced a 50 per cent. kill of mites. A water solution containing 0·5 mg. of I applied to the soil produced in 4 days a 50 per cent. kill of red spider mites on a french bean plant. Following a single spray application at 80 p.p.m. to small french bean plants, kills of adult and spider mites, with continued reinfestation, remained complete for more than 18 days. Absorption of the compound by foliage is rapid. I and related compounds show remarkable differences in toxicities to different groups of insects and mites. A. H. B.



I

Strychnine, The Total Synthesis of. R. B. Woodward, M. P. Cava, W. D. Ellis, A. Hunger, H. V. Daeniker and K. Schenker. (*J. Amer. chem. Soc.*, 1954, **76**, 4749.) The total synthesis of strychnine (I) identical in infra-red spectrum, melting point and chromatographic behaviour with the natural alkaloid is briefly reported. A. H. B.



I

Vitamin B_{12}, Degradation Product of. J. R. Cannon, A. W. Johnson and A. R. Todd. (*Nature, Lond.*, 1954, **174**, 1168.) Vitamin B_{12} was hydrolysed with sodium hydroxide and the resulting mixture of tetra-penta- and hexa-basic carboxylic acids as well as accompanying free nucleotide were separated by electrophoresis on paper. Of the three coloured fractions, that corresponding to the hexabasic acid was present in largest amount. This fraction was purified by sorption on and elution from Dowex 1X2 resin, and eventually obtained as a red crystalline solid (prisms). Later separation produced red needles; elementary analysis of the product gave the formula as $C_{47}H_{76}O_{16}N_6CoCl$. The ultra-violet absorption resembled that of vitamin B_{12}, excess of cyanide ions producing a bathochromic shift similar to that observed with vitamin B_{12}, indicating that the chromophore of the hexabasic acid was closely related to that of the vitamin. Details of the infra-red spectrum are given, a maximum at 4·67 μ indicating the presence of the cyanide ion. Absorption in the carbonyl region together with a strong inflexion in the 3 to 3·8 μ region are consistent with the polycarboxylic acid nature of the pigment. Strong aromatic bands in the 11·5 to 14·5 μ region are absent. It is thought that the red needles and prisms may be a polymorphic form of the same substance. J. B. S.

BIOCHEMISTRY

GENERAL BIOCHEMISTRY

Adrenaline and Noradrenaline in the Adrenal Medulla, Distribution of. O. Eränkö. *Nature, Lond.*, 1955, **175**, 88. In the cat, dog, rat, mouse and hamster it has been shown, using a fluorescent microscopical examination of formalin-fixed sections, that adrenaline and noradrenaline are present in separate cells of the adrenal medulla. In the rat a selective depletion of adrenaline was caused

by insulin whereas nicotine caused a release of noradrenaline. This was shown using the above technique and was in good agreement with the results obtained on biological estimation of the glands. M. M.

Organophosphorus Inhibitors, *In Vitro* Protection of Cholinesterases Against Some. W. K. Berry, K. P. Fellowes, P. J. Fraser, J. P. Rutland and A. Todrick. (*Biochem. J.*, 1955, **59**, 1.) Of 16 amino-acids investigated, only dopa (3:4 dihydroxyphenylalanine), abolished in high concentration the *in vitro* inhibition of horse serum cholinesterase by Sarin (*iso*propyl *P*-methyl phosphonofluoridate). This protective effect was exerted by catechol derivatives in general, among them adrenaline. Both horse serum and rat brain cholinesterases were protected against Sarin, dyflos (di*iso*propyl phosphorofluoridate), Tabun (ethyl-*NN*-dimethylphosphoroamidocyanidate) and *P*-ethyl-Sarin (*iso*propyl *P*-ethyl phosphonofluoridate). None of the oxidation products of dopa had protective activity greater than dopa itself. Evidence points to a reaction between the catechol and the anticholinesterase as the basis of the protective mechanism. In support of this Jandorf *et al.* (*J. Amer. chem. Soc.*, 1952, **74**, 1521) in similar experiments have isolated the reaction product of catechol and di*iso*propyl phosphorochloridate. G. P.

Pituitary Growth Hormone, Enhancement of Insulin Action by. P. H. Randle. (*Nature, Lond.*, 1954, **174**, 1053.) The possible dependence of the insulin-like action of growth hormone on the presence of insulin has been investigated by studying the influence of low concentrations of insulin and growth hormone upon the glucose uptake of the normal rat diaphragm surviving *in vitro*. The hemi-diaphragms of male albino rats, previously fasted for 20 hours, were incubated in Warburg manometers for three hours. They were then removed, blotted and weighed and the residual glucose determined in the incubation fluid. Glucose uptake was calculated as mg. glucose disappearing from the medium per g. of wet diaphragm per hour of incubation. The *in vitro* addition to the fluid of growth hormone alone had no influence on the glucose uptake of the diaphragm, but the presence of low concentrations of both growth hormone and insulin resulted in significantly greater uptake of glucose by the diaphragm than was produced by insulin alone. The results suggest that an action of growth hormone may be to accentuate the action of insulin in promoting the entry of glucose into the cell. G. F. S.

BIOCHEMICAL ANALYSIS

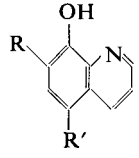
Lead in Blood and Urine, Determination of. S. P. Bessman, and E. C. Layne. (*J. Lab. clin. Med.*, 1955, **45**, 159.) The method is based on the formation of a red chloroform soluble complex with lead and diphenylthiocarbazone (dithizone). Two ml. of blood or 10 ml. of urine are placed in a glass stoppered Folin-Nessler tube, and add 5 ml. of digestion mixture (5 parts nitric acid plus 2 parts sulphuric acid v/v) and three glass beads. Digest over a microburner until the tube is filled with thin, white fumes. Take away the burner and add 20 drops of perchloric acid. Heat again through a colourless frothing stage until colourless and clear. Cool and add 5 ml. of water, 4 ml. of ammonium hydroxide and 1 drop of phenol red and mix. If the solution is not red add ammonium hydroxide dropwise until red. Now add 10 ml. of a buffer solution and 3 ml. of dithizone solution, stopper and shake. (The buffer solution is prepared by adding 75 ml. of concentrated ammonium hydroxide diluted to 250 ml., to 118 g. of dibasic ammonium citrate, cooling to room

temperature and adding 5 g. of potassium citrate and 2·5 g. sodium sulphite. Extract with 30 mg./l. dithizone in chloroform until the dithizone stays green and add 500 ml. of ammonium hydroxide.) Remove the supernatant by suction and add 10 ml. of wash reagent (consisting of 5 g. potassium cyanide plus 250 ml. of ammonium hydroxide diluted to 500 ml.). Remove the supernatant and then transfer the chloroform solution to a colorimeter tube 1 cm. in diameter, stopper with a cork and allow to stand for ten minutes until clear. Read the chloroform layer at 510 mμ against a chloroform blank. The dithizone lead colour shows a straight line relationship to the lead concentration in the original sample. Agreement between duplicate determinations on urine was 3·86 ± 2·61 per cent. and between duplicate blood levels 7·45 ± 4·20 per cent. Twelve determinations on the blood of patients with no history of exposure to lead gave a mean of 18·2 ± 11·2 μg. per 100 ml. with a range of 0 to 32 μg. Calcium ethylenediaminetetra-acetate at levels equivalent to 500 mg. per cent. in urine and 2500 mg. per cent. in blood does not interfere. G. F. S.

Sodium, Potassium and Chloride in Biological Material, Determination of. W. H. Hulet. (*Amer. J. med. Sci.*, 1955, **229**, 81.) A method is described for the determination of sodium, potassium and chloride in biological material and its application to food analysis. The food is homogenized in a Waring Blendor and 5 g. digested by boiling with 3 ml. of concentrated nitric acid A.R. The digested sample is transferred to a 100 ml. volumetric flask, filled to the mark with distilled water and filtered through Whatman No. 42 filter paper previously washed with 0·05N nitric acid. The concentration of sodium and potassium in the filtrate is determined by flame photometry. Chlorides are determined by the mercuric nitrate method. To 1 ml. of the food extract add 2 ml. of 0·1N nitric acid, 5 drops of diphenylcarbazone indicator and titrate with 0·05M mercuric nitrate solution from a microburette to the first appearance of a lavender colour. Excess mercuric nitrate deepens the colour to purple. The mercuric nitrate solution is standardised in the same way against 1·0 ml. of a 0·1M sodium chloride solution. G. F. S.

CHEMOTHERAPY

Antimalarial Agents; Synthesis of Quinolylaminoquinolinols. J. H. Burckhalter, W. H. Edgerton and J. A. Durden, Jr. (*J. Amer. chem. Soc.*, 1954, **76**, 6089.) Three isomeric quinolylaminoquinolinols (I, II and III) where R = $CH_2NC_5H_{10}$ and R′ = 7-chloro-4-quinolylamino, were synthesised in order to study the Schönhöfer theory of antimalarial action.



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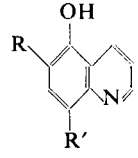

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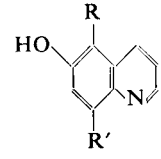

III

These compounds were tested against *Plasmodium lophurae* in the chick, and I, II and III were assigned respective quinine equivalents of 3·2, 0·15 and < 0·1. From the results it appears that a factor other than mere increased susceptibility to oxidation or quinone formation is important for high potency. A. H. B.

PHARMACOGNOSY

Datura Plants, Effect of Vitamin K and Naphthalene Acetic Acid on. T. Hemberg and B. Lowén. (*Svensk farm. Tidskr.*, 1954, **36**, 938.) Since the removal of the flowers from growing datura plants leads to a marked increase in the alkaloidal content of the leaves, an attempt was made to produce a similar effect by spraying the growing plants with synthetic hormones which were known to inhibit flower initiation. Naphthalene acetic acid (NE) was used, with and without the addition of Vitamin K as there was a possibility that the latter was necessary for the action of the hormone. The plants treated with Vitamin K alone showed the greatest increase in both fresh and dry weights, with the plants treated with NE + K, NE alone and the controls following in that order. The amount of alkaloid produced per leaf of the various plants increased in the same proportion as the dry weight, so that the percentage of alkaloid in the leaves (on a dry weight basis) remained practically constant in all the groups of plants. These differences in the dry weights and absolute alkaloidal contents between the variously treated plants were most marked in the early stages of growth, but were practically non-existent when the plants were mature. J. W. F.

Sulphanilamide, Acetylation of, in Plants. D. R. Jones and J. Wignall. (*Nature, Lond.*, 1955, **175**, 207.) Examination of the roots, stems and leaves of broad bean plants grown for 33 days with their roots immersed in an aqueous solution of sulphanilamide (100 μg./ml.) showed the presence of sulphanilamide in the leaves. There was little of the free drug in the roots, although bound drug could be revealed by hydrolysis and this was identified by chromatographic methods as acetyl sulphanilamide. Thus acetylation of sulphanilamide can occur in plant tissues as in animals. G. F. S.

PHARMACOLOGY AND THERAPEUTICS

Aldosterone and 9α-Fluorohydrocortisone Acetate in Rheumatoid Arthritis. L. E. Ward, H. F. Polley, C. H. Slocumb, P. S. Hench, H. L. Mason, V. R. Mattox and M. H. Power. (*Proc. Mayo Clin.*, 1954, **29**, 649.) This is a preliminary report on the use of these recently discovered steroids in patients with rheumatoid arthritis. Aldosterone (electrocortin) is an adrenocortical hormone isolated from extracts of whole adrenal glands of beefs and hogs and from the amorphous fraction of beef adrenal glands. It appears to be identical with a sodium-retaining corticoid present in human urine and may be that part of the amorphous fraction which has the greatest effect on the metabolism of electrolytes (hence the provisional name electrocortin). The chemical structure is closely related to that of corticosterone, the only difference being that at C–18 aldosterone has an aldehyde group whereas corticosterone has a methyl group. Both aldosterone and corticosterone lack the hydroxyl group at C–17 which characterises cortisone and hydrocortisone. The 9-halogen derivatives of hydrocortisone are key-intermediates in the synthesis of hydrocortisone from 11-epi-17-α-hydroxycorticosterone. All four derivatives (fluoro-, chloro-, bromo-, and iodo-derivatives) have been found to have adrenocortical-like activity, the most active being 9-fluoro-hydrocortisone acetate. Aldosterone was administered intramuscularly to 2 rheumatoid patients for 6 days each, as much as 800 μg./per day to one patient, and up to 1000 μg. per day to the other. The doses used produced no antirheumatic effects but did produce some retention of sodium, chloride and fluid. The 9α-fluorohydrocortisone acetate was administered to 3 rheumatoid patients in doses up to 4, 6 and 8 mg. by mouth daily

for 12 to 28 days. These doses lessened rheumatic symptoms but produced troublesome retention of sodium, chloride and fluid and loss of potassium. The changes were sufficient to cause œdema and hypopotassæmia with a tendency for the development of hypochloræmia and alkalosis. S. L. W.

Amidonitrothiazole in Trichomoniasis. S. R. M. Bushby, R. D. Catterall and M. Williamson. (*Brit. med. J.*, 1955, **1**, 78.) In this investigation the activity of the compound 2-formamido-5-nitrothiazole (291 C 51) was compared *in vitro* with that of 14 commonly employed antitrichomonal drugs; it was also used clinically in the treatment of 96 women with trichomoniasis, comparing the results with those obtained in 49 women using acetarsol. The examination *in vitro* showed that of the drugs previously recommended for the treatment of trichomonal vaginitis only penotrane and phenylmercuric acetate are somewhat more active than 291 C 51, and this applies especially to the rate at which they kill the organisms. Both of these drugs however have to be used in the relatively low concentration of 1:500 or less whereas 291 C 51 is used with only slight dilution and so has the higher therapeutic index. Compared with acetarsol it has about 100 times the activity *in vitro*. 291 C 51 was used clinically as a foaming pessary containing 100 mg. of the drug, 2 tablets were inserted high into the vagina nightly for 14 days; acetarsol, in the form of 250 mg. pessaries was employed in a similar manner for the same period. During treatment with either drug the signs and symptoms of vaginitis disappeared but in each series the relapse rate was high. The ultimate effect of treatment was not significantly different with either drug. None of the patients treated with 291 C 51 complained of toxic side-effects. The authors conclude that if the resistant character of trichomonal vaginitis, due either to failure to eradicate the infection or to unavoidable re-infection, necessitates prolonged and suppressive treatment, 291 C 51 has the advantages of being non-arsenical and non-toxic and is as effective as any non-arsenical drug at present available. S. L. W.

Barbiturate Antagonist, A New, β-Methyl-β-ethylglutarimide (Megimide, NP13). T. A. B. Harris. (*Lancet*, 1955, **268**, 181.) The rapid termination of pentobarbitone, thiopentone and barbitone anæsthesia by Megimide has been described by Shaw *et al.* (*Nature, Lond.*, 1954, **173**, 402), for mice, rats and rabbits. The drug has now been used clinically for the reversal of thiopentone anæsthesia. Fifty-seven psychiatric patients undergoing electric shock therapy, 6 patients undergoing orthopædic manipulation and 10 surgical cases were the subjects of the investigation. In the first two groups thiopentone was the only anæsthetic employed and reversal by Megimide (50 mg. i./v.) was rapid, the palpebral reflex returning in 30 to 60 seconds. The surgical cases were premedicated with hyoscine and omnopon and anæsthetised with thiopentone and *cyclo*propane. This group reacted more slowly to the antagonist, especially where anæsthesia was maintained for up to 40 minutes. This was attributed to the prolonged post-operative depression by the *cyclo*propane. In the complete series no side actions of Megimide were observed. G. P.

Cortisone, Inhibition of Acute X-Ray Damage with. L. E. Houghton, J. B. Walter and D. E. A. Jones. (*Brit. med. J.*, 1954, **2**, 1313.) A dose of 6000 r was delivered to a circular area of skin in 38 guinea-pigs. Twenty-four hours before the first exposure 19 of the animals received 10 mg. of cortisone acetate by subcutaneous injection; this was repeated each morning throughout the period of observation; the remainder were not given cortisone. 71 days after

the irradiation the 19 control animals showed large deep ulcers; the 19 cortisone-treated animals showed no ulcers. Erythema began on the 12th day and was present in 4 cortisone treated animals and 10 controls. During the next week epilation started and by the 32nd day all the control animals showed complete loss of hair on the irradiated areas, by which time 16 had also ulcerated. The skins of all 19 controls showed marked erythema during the period of epilation. In the case of the cortisone group the erythema was less pronounced and the hair tended to remain adherent. By the 32nd day 16 still showed incomplete epilation and 2 showed practically no hair loss. Not until the 42nd day had all the irradiated areas epilated. The results indicate that the administration of cortisone profoundly alters the response of skin to X-radiation. Since it is believed that tissue damage resulting from exposure to nuclear-fission products does not differ essentially from that produced by X-radiation it is possible that the protective action of cortisone might be extended to this field.

S. L. W.

β-Diethylaminoethyl Diphenylpropylacetate Hydrochloride, Effect of, on Barbiturates and Central Nervous System Depressants. L. Cook, E. Macko and E. J. Fellows. (*J. Pharmacol.*, 1954, **112**, 382.) Pre-treatment of male rats and mice with β-diethylaminoethyl diphenylpropylacetate hydrochloride (SKF 525-A) markedly prolonged the duration of hypnotic action of hexobarbitone, pentobarbitone, amylobarbitone, quinalbarbitone and butobarbitone. The hypnosis induced by Ortal, phenobarbitone or chloral hydrate was moderately prolonged, while that induced by barbitone, thiopentone, thioethamyl or methylpentynol was not affected by the drug. SKF 525-A had likewise no effect on induction time, minimal threshold anæsthetic concentration or duration of anæsthesia of either diethyl ether or nitrous oxide. These results are in agreement with previous findings that the mode of action is through the inhibition of some metabolising enzyme system.

G. P.

Digitalis, Activity of Diploid and Tetraploid Forms of. F. Hauschild and H. Wermann. (*Pharm. Zentralh.*, 1954, **93**, 363.) Determination of the mean lethal dosage of different forms of digitalis on guinea-pigs gave the following results:—

		MLD g./kg.	Moisture content per cent.
D. purpurea	2*n*	0·280 ± 0·013	75·21
D. purpurea	4*n*	0·324 ± 0·009	79·23
D. lanata	2*n*	0·126 ± 0·003	71·74
D. lanata	4*n*	0·277 ± 0·012	78·06

It is possible that the differences may be related to the higher water content of the 4*n* plants.

G. M.

Fluoride, Toxic Effect of. L. M. Carr. (*Nature, Lond.*, 1954, **174**, 884.) Sodium fluoride administered in drinking water to a group of rats was found to favour the initiation of a nutritional deficiency, thought to be due to lack of biotin. The rats were fed on a diet of 16 per cent. raw egg-white (to aid the onset of biotin deficiency), 10 per cent. casein, 67 per cent. sucrose, 4 per cent. lard and 3 per cent. salts, together with a suitable vitamin supplement. The experimental group of rats, receiving drinking water containing 80 parts per million of fluoride, showed significant weight losses after 16 days not shown by the corresponding control group, which did not receive fluoride. The fur of the experimental animals was bristled and rough, and there was alopecia of the

snout, head and legs, mild diffuse dermatitis and mild "spectacle eye." Increasing the vitamin A content of the diet, which was low, delayed the onset of the symptoms. Control experiments established that 120 p.p.m. of fluoride did not affect the growth of rats during a 7-week period, when a natural stock diet was fed. Loss in weight ceased as soon as egg-white was excluded from the diet. In another set of experiments orally ingested fluoride did not affect the severity of riboflavin deficiency. J. B. S.

Hexamethonium Bromide, Effect of, on the Pulmonary Circulation. O. Storstein and H. Tveten. (*Scand. J. clin. Lab. Invest.*, 1954, **6**, 169.) Hexamethonium bromide injected subcutaneously into 14 patients with various forms of heart disease, caused a significant fall in systemic arterial, pulmonary arterial and pulmonary capillary venous blood pressures. Cardiac output also fell, but heart rate, pulmonary arteriolar resistance and total peripheral resistance were not significantly altered by the drug. The pulmonary arterial pressure and pulmonary capillary venous pressure fell to the same extent, indicating that the hexamethonium was not selectively dilating the pulmonary arterioles. It was concluded that the reduction of pulmonary blood pressure by hexamethonium was due to a reduced venous return caused by pooling of blood in the systemic vascular bed. G. P.

Hexamethonium Bromide in Retard Medium. H. J. Goldsmith, D. W. Beaven and H. P. Lambert. (*Lancet*, 1955, **268**, 371.) 26 patients with severe hypertension were treated with injections of Vegolysen Retard, a 20 per cent. solution of hexamethonium bromide in polyvidone containing 1 in 1500 of ephedrine. 4 of 11 patients with malignant hypertension died within the first 3 weeks of treatment and in 6 of the 15 patients with benign hypertension treatment had to be discontinued within 4 months but in the other patients it was continued for 7 to 20 months. The hexamethonium was given by subcutaneous injection every 8 hours, the initial dose being 20 mg. The final dosage, usually ascertained after 3 to 4 weeks treatment, was from 80 to 400 mg., a common amount being 200 mg. After an initial 3 to 5 weeks in hospital, the patients administered the drug themselves, attending hospital at intervals for examination. In the group with benign hypertension, 8 patients returned to full-time work although 2 subsequently died. All patients having repeated attacks of cardiac dyspnœa remained completely free from attacks during treatment. Relief of headache was most satisfactory. Of the 7 patients with malignant hypertension who survived more than 3 months, 4 returned to full-time work, but 1 died after 50 weeks' treatment. In all the malignant cases treated for more than 3 months papillœdema disappeared; hypertensive retinitis in the benign cases did not improve. Figures are given for the fall in blood pressure. Constipation and postural faintness were the most frequent side effects, with diarrhœa and visual disturbances as the next in order of frequency. A few patients had difficulty in micturition and 2 had allergic rashes. Mild follicular sepsis was frequent and may have been due to bromism. Side effects were less common in patients with malignant hypertension and did not necessitate stopping treatment in any of them. Constipation and difficulty in micturition were conveniently counteracted by neostigmine bromide, 3·75 to 15 mg. by mouth. Patients with renal damage needed special care since the drug is excreted mainly in the urine. Formal comparison with a simple solution of hexamethonium bromide was not made but prolongation of action was not a striking feature of the retard preparation. Its important advantage was diminution of unpleasant side effects such as dizziness or exhaustion during the first hour after injection. H. T. B.

Histamine Antagonists, Effect of, on Oxytocic Action. F. G. Sulman. (*Arch. int. Pharmacodyn.*, 1954, **98**, 463.) The "oxytocic" effects of pituitrin, pitocin, ergotoxine, ergometrine, barium chloride, acetylcholine and carbamylcholine on the guinea-pig isolated uterus are not prevented by antihistamines. The antihistamines tested were diphenhydramine, tripelennamine, thenylpyramine, prophenpyridamine, chlorothen and doxylamine. The oxytocic effects of histamine were prevented in all cases and it is concluded that there is a difference in the mechanism of action of histamine and the other oxytocics on the uterus. G. F. S.

Isoniazid with Streptomycin or Sodium Aminosalicylate in Pulmonary Tuberculosis. Report of Tuberculosis Chemotherapy Trials Committee to the Medical Research Council. (*Brit. med. J.*, 1955, **1**, 435.) A detailed comparison is given of the results of treating pulmonary tuberculosis for 3 months with streptomycin plus two different dosages of isoniazid and of sodium aminosalicylate. Bacteriological findings in many patients treated for 6 months are also reported. The four treatments, denoted by symbols, were as follows. SH: Streptomycin 1 g. daily in 1 intramuscular injection, plus isoniazid 200 mg. daily in 2 equal doses by mouth. S2H: As SH, but streptomycin 1 g. given twice a week. 20PH: Sodium aminosalicylate 20 g. daily in 4 equal doses by mouth plus isoniazid 200 mg. daily in 2 equal doses by mouth. 10PH: As 20PH but only 10 g. daily of sodium aminosalicylate. Patients with acute rapidly progressive bilateral disease of recent origin were allocated to series SH or 20PH but others were allocated at random. 64 patients were excluded from the analysis of the results, and the numbers remaining in the survey were: SH 182; S2H 142; 20PH 159; and 10PH 105. 7 deaths occurred, 5 of them within a month of starting treatment. The toxicity of isoniazid during 6 months treatment was no greater than reported previously after 3 months. Treatment had to be stopped in 6 patients because of severe reactions attributed to sodium aminosalicylate and in 1 because of a severe reaction attributed to streptomycin. The majority of patients showed improvement after 3 months on any of the treatments and the differences between the 4 series were small having regard to general clinical condition, resolution of pyrexia, improvement in sedimentation rate and gain in weight. Independent assessment of the improvement in the radiographic appearance showed a statistically significant advantage for the SH series as compared with the 20PH or 10PH series. The proportions of patients bacteriologically negative at a single examination at 3 months were 75 per cent. in SH, 74 per cent. in S2H, 73 per cent. in 20PH, and 75 per cent. in 10PH. At 3 months bacillary resistance to isoniazid was found in 2/22 culture-positive SH patients, 12/30 S2H patients, 0/24 20PH patients, and 3/25 10PH patients. For streptomycin resistance the corresponding figures were 0/22 SH, 3/31 S2H, and for sodium aminosalicylate resistance 1/22 20PH and 1/23 10PH. Judged solely on the 3 months results, streptomycin 1 g. daily plus isoniazid 200 mg. daily is the most effective combination which has been used at any stage of the trial. The S2H treatment is less satisfactory in preventing the emergence of drug resistance and its use as a primary chemotherapeutic measure is not recommended. The 20PH and 10PH treatments were also effective, although not so powerful as SH. There is little to choose between 20PH and 10PH; either is a most valuable oral form of combined chemotherapy. In 240 patients the trial was continued for 6 months and confirmed the adequacy of the SH, 20PH and 10PH regimes, and the inadequacy of the S2H regime, in preventing the development of drug resistance. A small group of patients with sodium aminosalicylate

resistant organisms when treatment commenced were not protected from developing isoniazid resistance by either of the PH regimes. H. T. B.

2-Mercaptoglyoxalines, Antithyroid Activity of Derivatives of. A. Lawson and C. E. Searle. (*Biochem. J.*, 1955, **59**, 345.) A range of substituted 2-mercaptoglyoxalines were tested for antithyroid activity in rats by the determination of the effect of a single dose of the drug on the radioactive iodine uptake of the rat thyroid gland over a 4 hour period. Seventeen compounds were tested in the 2-mercaptoglyoxaline series; all 4-substituted 2-mercaptoglyoxalines were less active than 2-mercaptoglyoxaline, the most active being the *n*-butyl derivative. *S*-Acyl 2-mercaptoglyoxalines (4 compounds tested) were active but *S*-alkyl derivatives (8 compounds tested) showed only weak activity. In a series of tests with ergotamine tartrate a reduced thyroidal uptake was found, a sex difference sometimes being observed. Dihydroergotamine methanesulphonate had no effect on the uptakes of either male or female rats. R. E. S.

Methylpentynol and Anticonvulsant Drugs. Anti-Leptazol Efficacy of Combinations of. D. A. Brodie, A. Tye and J. W. Nelson. (*J. Amer. pharm. Ass., Sci. Ed.*, 1955, **44**, 59.) Tests were carried out to determine the protective effect in mice of a series of anticonvulsant preparations against a lethal dose (120 mg./kg.) of leptazol (pentetrazol) injected subcutaneously at the time of peak effect of the protective substance. The neurological toxicity of the anticonvulsant preparations was assessed by a test depending on the ability of an animal to walk a narrow cage rim and maintain its equilibrium. The protective index (TD50/PD50) was calculated and used as a criterion of safety. Phenobarbitone had the greatest margin of safety, followed by trimethadione, methylpentynol and paraldehyde. Mixtures of methylpentynol with phenobarbitone or paraldehyde had a protective index intermediate between that of the components, while for the mixture of methylpentynol with trimethadione, the protective index was lower than that of either component. Although methylpentynol has been reported to potentiate the action of phenobarbitone, the mixture of these substances had a lower margin of safety than phenobarbitone alone. G. B.

Morphine Antagonists. F. H. Shaw and A. Shulman. (*Nature, Lond.*, 1955, **175**, 388.) Tetrahydroaminacrin and 2:4-diamino-5-phenylthiazole have been shown to possess an antagonistic action to the depressant effects of morphine in rats. This paper reports the antagonistic effects of the thiazole derivative to morphine in 5 patients suffering intolerable pain in the terminal stages of carcinoma. Each had been receiving 3 grains of morphine daily in divided doses at 2 to 4 hour intervals which had not given complete relief. The patients were now given as much as 1½ grains of morphine in one injection, and the severe respiratory depression and narcosis which followed were relieved by an injection of up to 40 mg. of the antagonist. The analgesic effect of the morphine was not affected, the patients remaining free from pain for 12 hours or more. The respiratory depression was relieved first, followed by a lessening of the narcosis as the dose of the thiazole derivative was increased. Large doses awakened the patient, but the duration of relief was shortened. Over the period of testing, 6 to 10 weeks, no evidence of tolerance to either morphine or the antagonist was found. The latter had no disagreeable side effects in doses of 5 to 10 times the therapeutic level, and differed from nalorphine in that it did not provoke withdrawal symptoms in patients already receiving morphine, and is therefore not a complete antagonist. J. R. F.

Tetanus Toxin, Mode of Action of. V. B. Brooks, D. R. Curtis and J. C. Eccles. (*Nature, Lond.*, 1955, **175**, 120.) An investigation of the action of tetanus toxin on synaptic inhibition has confirmed the observations of Sherrington that tetanus toxin acts on the spinal cord similarly to strychnine, but both these substances act, not by converting synaptic inhibition into excitation, but by suppressing all types of synaptic inhibition. This probably explains the general tetanus as the toxin spreads throughout the whole nervous system.

G. F. S.

Thiouracils, Antithyroid Activity of Some *S*-Substituted. H. W. Barrett, and G. L. Elliott. (*Science*, 1955, **121**, 62.) A number of thiouracil derivatives containing a thioether linkage with or without the *S*-substituent, have been tested for antithyroid activity. The compounds were given to male rats in the food and compared with thiouracil. The effects were determined by measuring changes in the weight and iodine content of the thyroid glands. The *S*-substituted thiouracils were not antithyroid compounds as such but first have to undergo cleavage to free the *S*, which is probably brought about by enzymatic attack.

G. F. S.

BACTERIOLOGY AND CLINICAL TESTS

Diphtheria Toxin, Potent. S. Nishida. (*Nature, Lond.*, 1954, **174**, 970.) The author by using shaking cultures for *C. diphtheriæ*, obtained physiologically young cells containing the highest toxicities yet found. The shaker rotated at approximately 130 cycles/min. with an amplitude of 13 cm. A series of 200 ml. flasks each containing 20 ml. of Pope's medium was sampled in the three stages of growth: log phase, phase of negative acceleration and maximum stationary phase. The bacilli harvested were washed with water, suspended in thiomersalate solution (0·01 per cent.) and were tested for toxicities by subcutaneous or intraperitoneal injection. The toxin content of the bacilli was highest in the period of decelerating rate of multiplication, about 200 to 350 MLD/mg. of nitrogen being usually obtained. The toxicity obtained was identified by the findings at adrenal glands of injected guinea-pigs and by the neutralisation test by diphtheria antitoxin.

J. R. F.

Ultra-violet Radiation, Bactericidal and Fungicidal Effects of. F. O. Gundersen and O. G. Clausen. (*Medd. Norsk Farm. Sels.*, 1954, **11**, 127, 151; 1955, **12**, 1.) The sensitivity of 10 strains of fungi and 33 of bacteria to ultra-violet radiation has been studied. Details of the methods are given. Very high death rates were observed for all non-sporulating bacteria, and excellent results were obtained against ærobic and anærobic spore-forming bacteria and also most of the fungi. The amounts of energy in ergs/sq. cm. required to achieve 100 per cent. elimination by ultra-violet radiation were in many cases higher than reported elsewhere, however, most of the earlier reports are based on 90 per cent. elimination. The authors were unable to confirm the opinion of others that vegetative cells and bacterial spores are equally susceptible to ultra-violet radiation. Attention is drawn to the high death rate of *Proteus vulgaris* and *Pseudomonas aeruginosa*. It is suggested that selected elimination of these 2 organisms by ultra-violet radiation from material containing certain other bacteria may be possible. It is stressed that the death rates observed are not strictly comparable to those of airborne micro-organisms because of the different physical conditions.

J. R. F.