# ABSTRACTS OF PAPERS PUBLISHED IN OTHER JOURNALS

## CHEMISTRY

### ANALYTICAL

**Aminosalicylic Acid, Sodium Aminosalicylate and Commercial Preparations, Non-aqueous Titration of.** L. G. Chatten. (*J. Amer. pharm. Ass., Sci. Ed.*, 1956, **45**, 556.) For the assay of *p*-aminosalicylic acid, a sample of 80 to 100 mg. is dissolved in 50 ml. of acetone using a magnetic stirrer, and titrated with a 0·1N solution of potassium hydroxide in methanol, using thymol blue as indicator and titrating to the blue end point. Tablets should be powdered and a sample of powder stirred for 10 minutes with 40 ml. of acetone. After filtering and washing the residue with acetone, the filtrate and washings are mixed and titrated as above. The procedure recommended for sodium *p*-aminosalicylate is similar except that a 40 to 50 mg. sample is dissolved in 50 ml. of anhydrous methanol and titrated with 0·05N perchloric acid in dioxan, using thymol blue and titrating to the peach end point. In both cases the colour change is sharp and coincides with the potentiometric end point. The method is rapid, accurate and less troublesome than the method of titration with nitrite and an external indicator. G. B.

**Aureomycin Hydrochloride and Tetracycline Hydrochloride in Aureomycin Hydrochloride, Assay for.** F. S. Chiccarelli, P. Van Gieson and M. H. Woolford Jr. (*J. Amer. pharm. Ass., Sci. Ed.*, 1956, **45**, 418.) Aureomycin may be determined by measurement of the blue fluorescence formed when an alkaline solution is excited by filtered ultra-violet radiation. Small quantities of tetracycline, if present, do not interfere in the determination. Tetracycline, when examined in alkaline solution has an absorption maximum at 380 mμ; solutions containing at least 0·2 mg. of aureomycin per ml. in 0·25N sodium hydroxide exhibit a shelf at 380 mμ in the absorption spectrum, proportional in height to the concentration of tetracycline present, and this is the basis of a method for the determination of small quantities of tetracycline in aureomycin. G. B.

**Carbon Disulphide in Piperazine Compounds, Determination of.** R. E. Booth and E. H. Jensen. (*J. Amer. pharm. Ass., Sci. Ed.*, 1956, **45**, 535.) Carbon disulphide may be liberated from its piperazine compound by acid hydrolysis, separated by extraction with chloroform and determined spectrophotometrically as follows. A sample equivalent to about 0·12 g. of piperazine-carbon disulphide equimolecular complex is placed in a 200-ml. pressure bottle and shaken for one minute with 100 ml. of chloroform and 10 ml. of 14N sulphuric acid. The bottle is closed and heated in a water bath at 70° for at least 10 minutes. After cooling in water a quantity of the chloroform solution is withdrawn from below the acid layer through a chloroform-washed plug and the light absorption measured at 319 mμ against a chloroform blank. The concentration of carbon disulphide in g./litre is calculated from the absorption index of carbon disulphide in chloroform (1·11). The assay has also been applied successfully to 2-methyl and 2:6-dimethylpiperazine-carbon disulphide, and to a commercial product consisting of piperazine-carbon disulphide in an inert diluent. G. B.

**Tetracycline Hydrochloride and Aureomycin Hydrochloride in Tetracycline Hydrochloride, Assay for.** M. H. Woolford Jr. and F. S. Chiccarelli. (*J. Amer. pharm. Ass., Sci. Ed.*, 1956, **45**, 400.) Small amounts of aureomycin present in tetracycline cannot be estimated fluorimetrically because the fluorescence is quenched by the relatively large amount of tetracycline. The proposed method depends upon the determination of tetracycline by measurement of the ultra-violet absorption at 380 mμ in alkaline solution. Under these conditions aureomycin is rapidly destroyed and quantities up to 20 per cent do not affect the result. The quantity of aureomycin may then be calculated from the ultra-violet absorption of an acid solution at 355 mμ, after correcting for the absorption due to tetracycline at this wavelength. G. B.

**Three Tetracyclines, Identification Tests for.** A. Fouchet. (*Ann. pharm. franç.*, 1956, **14**, 281.) Place 2 ml. of a 50 per cent solution of zinc chloride in a small porcelain dish and heat until a skin forms. Add a very small quantity of the substance under test and continue heating for 1 minute. Aureomycin gives a garnet-red residue similar in colour to chromic acid, which dissolves in water acidified with acetic acid to give a solution the colour of dichromate. Tetracycline gives a yellow precipitate, soluble in water to give a solution the colour of potassium chromate. Oxytetracycline yields a violet (amethyst)-coloured residue, soluble in water acidified with acetic acid. G. B.

# BIOCHEMISTRY

## GENERAL BIOCHEMISTRY

**Oxytocin, Synthesis and Biological Activity of a New Potent Analogue of.** R. A. Boissonnas, St. Guttmann, P. A. Jaquenoud, J. P. Waller, H. Konzett and B. Berde. (*Nature, Lond.*, 1956, **178**, 260.) The preparation of a structural analogue of oxytocin by replacing the *iso*leucyl group by a valyl group is described. 'Valyl-oxytocin' was assayed by several methods, the international post-pituitary standard powder being used for comparison throughout. The effect on the blood pressure in the chicken and on the isolated uterus was equivalent to that of 3 I.U./ml. However, by measuring the milk ejection pressure of the rabbit mammary gland, the effect was equivalent to that of 15 I.U./ml. On the cat uterus *in situ*, the effect was equivalent to that of 16 I.U./ml., whereas on the cat uterus *in vitro* it was equivalent to that of 6 I.U./ml. In non-anaesthetised rats, 'valyl-oxytocin' had an antidiuretic effect equivalent to that of 0·03 I.U./ml. In spinal cats its pressor activity was approximately equivalent to that of 0·015 I.U./ml. The relationship between the pressor activity and the uterine activity of 'valyl-oxytocin' is therefore even more in favour of the uterine activity than is the case with natural and synthetic oxytocin.

A. H. B.

## BIOCHEMICAL ANALYSIS

**Barbiturates in Biological Material, Detection, Estimation and Identification of.** P. M. G. Broughton. (*Biochem. J.*, 1956, **63**, 207.) A rapid method is described for the determination and identification of barbiturates in biological material. For estimation in blood, extract 5 to 10 ml. three times with 30 ml. of chloroform, pass the combined extracts through a filter paper into a separating funnel and extract with 5 to 10 ml. of 0·45N sodium hydroxide. Separate and clear the aqueous layer by centrifuging. With urine, gastric contents etc. take 10 to 25 ml., acidify with sulphuric acid, extract as above, but wash the

chloroform extracts with 5 ml. of phosphate buffer before filtering to remove salicylates which may be present. Tissues may be extracted by homogenising with the chloroform. The clear sodium hydroxide extract is now hydrolysed by heating 5 ml. in a calibrated tube for 15 minutes in a water bath, cooled and made up to 5 ml. For measurement 2 ml. quantities of the extract are added to 2 ml. of 0·45N sodium hydroxide and to 2·0 ml. of 0·6M–$H_3BO_3$–KCl. The extinction $E_N$ and $E_B$ of these two solutions are measured from 227 to 265 m$\mu$, paying particular attention to the wavelengths at which maxima, minima and isosbestic points occur. The criteria for the spectrophotometric detection of barbiturates are, maximum at 238 to 240 m$\mu$ in borate, maximum at 252 to 255 m$\mu$ and minimum at 234 to 237 m$\mu$ in sodium hydroxide, isosbestic points at 227 to 230 and at 247 to 250 m$\mu$. The greatest differences between $E_N$ and $E_B$ are at 260 m$\mu$ (positive) and 236 m$\mu$ (negative). The determination of barbiturate depends on the fact that, at 260 m$\mu$, $E_N = E_B$ for extracts containing no barbiturate. Partial identification of barbiturates, particularly between short, intermediate and long acting, can be made by measuring their decomposition in alkali. Solutions in 0·45N sodium hydroxide are heated in a boiling water bath and the percentage, R, of barbiturate remaining after a given time is found by measuring $E_N - E_B$ at 260 m$\mu$ before and after hydrolysis. R varies from 31·8 for phenobarbitone to 98·2 per cent for pentobarbitone after 15 minutes hydrolysis. A complete analysis can be made in one hour. G. F. S.

**Parathion in Biological Material, Isolation and Identification of.** A. Fiori. (*Nature, Lond.*, 1956, **178**, 423.) Most of the methods used for the isolation of parathion from biological material have defects which result either in a small yield of the material or in a very impure material. Among the identification methods, the Averell and Norris reaction has proved non-specific while ultra-violet spectrophotometry and paper chromatography are affected by the impurities present in the extracts. In devising a new system of isolation and identification, a preliminary extraction is made by treating the tissue with a mixture of ethanol, trichloroacetic acid and water. After centrifugation the supernatant fluid is filtered, the ethanol evaporated off and the aqueous solution is passed through a column of acid alumina. No visible rings formed but the parathion was completely adsorbed, while many impurities remained in the aqueous solution. The parathion is then eluted from the alumina with ethyl ether. The ether is filtered and evaporated. The residue is dissolved in benzene or ethanol and chromatographed. Development is carried out with the ascending method using 5 per cent ethyl ether in water-saturated light petroleum as solvent. The spots of the parathion and of its breakdown product, *p*-nitrophenol, are detected by two ultra-violet lamps, one at 3600 Å and the other at 2537 Å. With the 3600 Å lamp the *p*-nitrophenol absorbs strongly, while the parathion absorbs weakly. With the 2537 Å lamp the parathion absorbs strongly; 0·5 $\mu$g. being easily detectable. The parathion has an $R_F$ value of 0·98 and *p*-nitrophenol has a value of 0·30. M. M.

## CHEMOTHERAPY

**Oils, *In Vitro* Antibacterial Activity of.** J. C. Maruzzella and M. B. Lichtenstein. (*J. Amer. pharm. Ass., Sci. Ed.*, 1956, **45**, 378.) Oils were tested against 10 organisms by a method in which a disk of filter paper moistened with the oil was placed on a seeded nutrient agar plate and incubated, the zone of inhibition being measured after 24 hours at 37°. Of 110 volatile oils examined, eucalyptus, birch tar, cinnamon and cedar leaf oils and balsam of tolu showed the greatest

antibacterial activity. Birch tar, parsley seed, valerian, eucalyptus, pennyroyal and rosemary oils and balsams of tolu and Peru were effective against 8 or more of the test organisms. Cajuput, copaiba, garlic, hops, expressed laurel, myrrh, niaouli, nutmeg, origanum and savory oils showed no antibacterial activity. Of the test organisms used, *Bacillus subtilis* was the most sensitive and *Aerobacter aerogenes* the most resistant to the effect of volatile oils. G. B.

## PHARMACY

**Antacids, *In Vitro* Study of.** J. J. Hefferren, G. Schrotenboer and W. Wolman. (*J. Amer. pharm. Ass., Sci. Ed.*, 1956, **45**, 564.) Seven commercial antacid tablets were examined by four methods of testing *in vitro*. The preparations included dried aluminium hydroxide gel, magnesium trisilicate, aminoacetic acid, calcium carbonate, dihydroxy aluminium aminoacetate, dihydroxyaluminium sodium carbonate and hydroxyaluminium magnesium aminoacetate. The tests methods employed included those of Hammarlund and Rising, and Dale and Booth, in which a test dose is placed in the test medium, and fresh medium added at intervals. In the method of Johnson and Duncan, part of the test medium is removed from time to time and fresh medium added. This method and a modification of it were also used. Results obtained by the various methods differed widely, but the same order of effectiveness was established for all the preparations irrespective of the test method employed. In a comparative study of various artificial gastric juices and pooled human gastric juice for testing purposes, it was shown that the addition of mucin to simulated gastric juice U.S.P. gave a product with a titration curve and antacid response similar to human gastric juice. G. B.

**Antibiotics, Comparative Release of, from Ointment Bases.** H. J. Florestano, M. E. Bahler and S. F. Jeffries. (*J. Amer. pharm. Ass., Sci. Ed.*, 1956, **45**, 538.) The extent to which antibiotics are released from ointments was assessed by measuring their potency by the agar cup-plate method against a number of organisms common in cutaneous infections (*Proteus vulgaris*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Staphylococcus aureus* and *Streptococcus pyogenes*). Bacitracin, polymyxin B sulphate, neomycin sulphate and mixtures of these antibiotics were incorporated in two ointment bases and examined by this method. In all cases the release of antibiotic was considerably greater from a water-miscible base "Fuzene"—containing liquid paraffin 10, white soft paraffin 10, Glycowax S-932 ("polyhydric alcohol fatty acid") 10, polyethylene glycol 400 distearate 10 and polyethylene glycol dilaurate 60, than from a greasy base consisting of soft paraffin, mineral oil and lanolin.

G. B.

**B.C.G. Vaccine, Freeze-dried.** J. Ungar, P. Farmer and P. W. Muggleton. (*Brit. med. J.*, 1956, **2**, 568.) A method is described for the production of a viable B.C.G. vaccine by freeze-drying a suitable suspension of cells in 8·3 per cent dextran with 7·5 per cent glucose. The B.C.G. organisms for vaccine production can be grown in deep culture in Sauton's medium with 0·025 per cent triton WR 1339—a non-ionic polyoxyethylene ether—without affecting their biological properties. By the incorporation of this wetting agent in the culture medium a deep growth of the B.C.G. develops as unclumped cells which disperse well on shaking. This makes it possible to dispense with the milling process necessary to produce a homogeneous suspension from a surface growth and which may result in the retention of small clumps and render bacteria more vulnerable to the stress of freeze-drying. The bacteria, which are uniformly

dispersed, can be easily harvested in the centrifuge and the deposit resuspended in dextran-glucose solution. The freeze-dried vaccine produced in this way is a safe and reasonably constant product. Owing to its long storage life it can be accurately standardised before issue on the basis of its viable-cell content, and each batch can also be checked for virulence. In addition each batch can be tested for its tuberculin-converting power and for its freedom from toxicity as judged by the absence of excessive local lesions after injection into guinea pigs. A study of the keeping properties of the dried vaccine has shown that it has a life of at least 12 months when stored below 20°. S. L. W.

**Hydrophilic Ointment Bases, Release of Medication from.** D. Y. Barker, J. E. Christian and H. G. DeKay. (*J. Amer. pharm. Ass., Sci. Ed.*, 1956, **45**, 601.) Radio-active iodine ($^{131}I$) was obtained from sodium radio-iodide solution and incorporated with iodine and potassium iodide in the ointment bases under examination. The activity, expressed as counts/minute, was determined on an accurately-weighed sample of each ointment. Petri dishes of nutrient agar were prepared but the medium was not seeded with a test organism. One cup containing a weighed amount of ointment was placed on each agar plate. The dishes were incubated at 37° for 24 hours, after which strips of agar were removed and the radioactivity measured. Corrections were applied for background and decay, and the proportion of iodine released to each part of the plate calculated. Compared with the usual method of examining ointments by measuring zones of inhibition on agar plates seeded with a suitable test organism, the radioactive tracer method has the advantage of measuring the actual quantity of medicament released from the ointment and its distribution in the agar. Tests were carried out using hydrophilic ointment U.S.P.XIV, and similar ointments in which the sodium lauryl sulphate was replaced by other surface-active agents. In all cases the iodine was found to have diffused throughout the agar medium. The maximum release of iodine was obtained when the concentration of surface-active agent was 1 per cent for sodium lauryl sulphate Ethomid C/15 or Brij 35, or 5 per cent for G-7596-J. The same trend was observed using the seeded plate technique, but whereas the U.S.P.XIV ointment gave the smallest zone of inhibition, the radioactive tracer method revealed that the release of iodine from this base was the greatest. G. B.

**Silicone-Rubber Tubing in Blood Transfusion.** J. F. Wilkinson, G. G. Freeman, N. New and R. B. Noad. (*Lancet*, 1956, **271**, 621.) The results of 296 transfusions of whole blood, packed cells, and serum through seven types of silicone-rubber tubing are reported. In the course of these transfusions only 3 reactions (1·01 per cent occurred). This incidence of reactions is of the same order as has been observed with natural rubber tubing under similar conditions at the same hospital. Because of its resistance to repeated sterilisation, its relatively long life in good condition, its transparency, and its physiological inertness, silicone rubber is considered superior to natural rubber for blood-transfusion work and is recommended for this purpose. Silicone-rubber tubings were found to be in satisfactory condition for further use after over 40 transfusions, while natural rubber tubings under similar conditions showed much deterioration after 6 to 12 sterilisations. The most satisfactory compositions of silicone rubber so far examined are a dimethylpolysiloxane gum filled with either an amorphous precipitated silica or a pyrogenic silica. S. L. W.

**Tablet Granulations, Porosity of.** W. A. Strickland Jr., L. W. Busse and T. Higuchi. (*J. Amer. pharm. Ass., Sci. Ed.*, 1956, **45**, 482.) The true density of tablet granulations was determined by preparing tablets with punches

set at a little over 7000 kg./sq. cm., so as to remove all void space, weighing the tablets and calculating the volume from their dimensions. The apparent density was determined by weighing the granules in air and in mercury at various pressures, and extrapolating to low pressures of mercury at which all intergranular spaces are filled but no mercury has entered the granules. Void space was low (about 3 per cent) in an acetylsalicylic acid granulation prepared by precompression and in granular potassium bromide (about 5 per cent). Granules prepared by moist granulation with starch paste contained about 30 per cent of void space. G. B.

## PHARMACOLOGY AND THERAPEUTICS

**Amiphenazole in Obstetric Analgesia.** J. M. Holmes. (*Lancet*, 1956, **2**, 765.) Morphine grains ½ and amiphenazole 30 mg. were given intramuscularly to 20 patients in strong labour. Six of the patients were delivered within 2 hours, and 5 of the babies cried immediately. Nine were delivered from 5 to 7 hours after the injection, and 6 of the babies had difficulty in breathing and became cyanosed; and 9 babies of the 20 patients receiving the mixture showed definite but reversible respiratory depression. From this trial it was concluded that the action of amiphenazole is less prolonged than that of morphine and its duration of effective action is probably about 4 hours. 30 other patients were given morphine grains ¼ and amiphenazole 30 mg. If the cervix became fully dilated within 8 hours, a further dose of amiphenazole 30 mg. was given intramuscularly. Only 4 of the babies became cyanosed and showed evidence of respiratory depression. Each of these depressed babies received amiphenazole 3 mg. intravenously into the umbilical vein and respiration was fully established within 6 minutes of birth. Of the 50 patients in the trial only 1 developed vomiting attributable to morphine, and 6 others, who normally vomited after morphine, experienced mild nausea only. Slowing of maternal respiration was not observed. Narcosis was greater than after pethidine but much less than after morphine used alone; there was more amnesia than after pethidine. Uterine contractions became less frequent but were not reduced in strength, and the progress of labour, and the cervical dilatation, appeared to be accelerated. No adverse side-effects were observed. The author concluded that amiphenazole much reduces the undesirable qualities of morphine without significantly reducing its analgesic action on the mother, and in the doses recommended can reduce, though not completely eliminate, neonatal apnoea caused by morphine. S. L. W.

**Antihistamines, Physical Properties and Pharmacological Activity.** N. G. Lordi and J. E. Christian. (*J. Amer. pharm. Ass., Sci. Ed.*, 1956, **45**, 300.) The ionisation constants, solubilities at pH 7·4 at 37·5° and relative surface activities at pH 7·4 were determined for a series of 16 commercial antihistamines. The constants of procaine and papaverine were also determined for purposes of comparison. There was no apparent correlation between any of the properties investigated and the antihistamine activity. It is concluded that antihistamine activity is a highly specific effect, the influence of the physical properties of the drug being concerned with access to the site of action, forces which tend to bind the drug to the receptor, and persistence of effect. It was observed that the least soluble antihistamines are among the least toxic and have the slowest onset of action and the most prolonged effect. G. B.

**Benactyzine Derivatives, Potentiating Effect of, on Anaesthesia in Mice.** C. H. Holten and V. Larsen. (*Acta pharm. tox. Kbh.*, 1956, **12**, 346.) The prolonging effect of a series of compounds, related to benactyzine, adiphenine and

diphenhydramine, on hexobarbitone anaesthesia in mice has been studied. The compounds to be tested were given intraperitoneally to groups of ten mice at ascending dose levels and thirty minutes later all groups and a control group were given 100 mg. per kg. of hexobarbitone intraperitoneally. By comparing the prolongation of the sleeping times to the controls and relating this to the log dose, the index of activity was calculated. Most of the compounds were also tested for spasmolytic effects on spasms induced on the guinea pig isolated ileum with histamine, acetylcholine or barium chloride, and also for acute toxicity in mice. The results showed that the activities of a number of benzilic esters of amino alcohols, especially ethylaminoethanol, dimethylaminoethanol, diethylaminoethanol (benactyzine) and diethylamino*iso*propanol were very high and the compounds also had strong anticholinergic effects. Derivatives of benactyzine in which the tertiary alcoholic group in the benzilic acid moiety of the molecule was altered showed the chlorine compound to be as active as benactyzine. When the tertiary alcohol group was etherified, activity was somewhat decreased, while esterification decreased the effect considerably. Diethylaminoethyldiphenylpropyl acetate (SKF 525-A) also had a considerable action. Adiphenine and trasentin had very little effect. Diphenhydramine and related compounds had a moderate effect, while chloro-substitution in the phenyl group increased the activity without increasing toxicity. Of the common drugs, methadone, pethidine and chlorpromazine were active. Chlorpromazine was as active as benactyzine while reserpine was considerably more active. In contrast the quaternary ammonium compounds were inactive. G. F. S.

**Carbutamide (BZ55) in Diabetes, Clinical Trial of.** L. J. P. Duncan, J. D. Baird and D. M. Dunlop. (*Brit. med. J.*, 1956, **2**, 433.) Carbutamide (*N*-butyl-*N'*-sulphanilylurea), a hypoglycaemic compound which is active when given by mouth, was studied in patients over the age of 45 suffering from mild diabetes who were not more than 10 per cent over their ideal weight but whose hyperglycaemia and glycosuria could not be eliminated by dietary restrictions alone. The trial was completed in 44 patients of whom 22 were studied in hospital for 20 days and 22 were kept in hospital for 8 days. Carbutamide was started on the 8th and 4th day respectively, dosage being adjusted in accordance with the clinical response. Diets were individually prescribed, and for each patient the same meal each day contained a constant calculated quantity of calories, carbohydrate, fat and protein. Blood sugar was determined 3 times daily and glucose tolerance was measured during the initial control period and again after 5 or 10 days treatment. Haemoglobin determinations and white cell counts were made, and liver function tested. The initial dose given to the first 12 patients was 3 g. of the drug in 0·5 g. tablets before breakfast. The remaining 32 received 4·5 g. If the response was satisfactory the daily dose was gradually reduced over a few days to 1·5 g. and if it continued to be satisfactory the patients were discharged on a daily dose of 1–1·5 g. Of the first group of 22 patients 16 responded favourably; symptoms were abolished, blood-glucose levels were satisfactory and glycosuria was reduced by at least 75 per cent of the control values. 6 patients were unresponsive to the drug. In the second group also 16 patients responded satisfactorily; 3 showed some but not adequate response and 3 were entirely unresponsive even to large doses of the drug. The 32 responsive patients were observed as out-patients for periods of from 4–18 weeks. All remained free from diabetic symptoms; in 2 the dose had to be reduced to 0·5 g. daily because of hypoglycaemic symptoms. In 12 patients who were given dummy tablets the blood glucose level and glycosuria began to increase within 2 weeks; good control was again achieved

within 1 week of recommencing treatment. Side effects consisting of mild headache, malaise and drowsiness occurred in a few patients receiving the larger initial dose but disappeared on reducing the dose to maintenance levels. One case of drug fever occurred necessitating temporary cessation of treatment. In 3 cases a sulphonamide rash appeared but regressed spontaneously. No interference with liver function was noted. There was a definite granulocytopenia during the initial 2 weeks of treatment but in most cases the count returned to normal on the maintenance dosage. There was evidence of a toxic effect on the blood platelets and there is a possibility that thrombocytopenia may occur with alarming frequency. The drug may provide a welcome alternative to insulin in a limited group of middle-aged or elderly non-obese patients whose diabetes cannot be satisfactorily controlled by dietary restrictions alone but further study is necessary before it is used generally. H. T. B.

**Carbutamide (BZ55) in Diabetes, Trial of.** F. W. Wolff, G. A. Stewart, M. F. Crowley and A. Bloom. (*Brit. med. J.*, 1956, **2**, 440.) A detailed study was made of the use of carbutamide in the treatment of 45 diabetics. The group included a preponderance of middle-aged or elderly female patients. In 34 the need for insulin had previously been established; 7 were new cases who would normally have received insulin and 4 were patients who had been controlled for several years by diet alone but were now showing signs of needing insulin. The patients were kept in hospital for 2 weeks and then observed twice weekly. For the first 5 days they were maintained by diet alone without insulin. On the next two days breakfast was omitted and on the second day carbutamide was given in a dose of 55 mg./kg. body weight (2·5 to 3·5 g. per patient). On the second day of treatment the patients were given 2 g. of the drug and on subsequent days 1 g. daily as in-patients for 5 days and continued as out-patients if the response was satisfactory. Sugar and sulphonamide levels in the blood and urine were determined 3- or 6-hourly. In 19 patients the blood-sugar levels fell to within normal limits and glycosuria disappeared either during the period in hospital or during the follow-up period. In the remaining 26 patients administration of the drug caused a significant drop from the fasting blood-sugar levels but failed to prevent hyperglycaemia and glycosuria; increasing the dose three-fold did not reverse the trend. In 5 patients a typical sulphonamide skin rash occurred. The response to carbutamide was not related to the duration of the diabetes but the successful cases generally gave a history of diminishing insulin requirements. As the drug exerted no control over the post-prandial rise in blood-sugar its action is probably on the mechanism controlling the utilisation of endogenous glucose. H. T. B.

**Carbutamide (BZ55) in Treatment of Diabetes.** J. M. McKenzie, P. B. Marshall, J. M. Stowers and R. B. Hunter. (*Brit. med. J.*, 1956, **2**, 448.) Carbutamide was used for the treatment of 20 patients with mild diabetes. 16 needed small doses of insulin and had never known ketosis; 4 required insulin to avoid ketosis. Detailed studies were made of 10 in-patients. They were treated for an initial period by dietary restrictions alone until no further improvement could be obtained or hyperglycaemia was increasing. A high loading dose of carbutamide was then given over 3 days followed by maintenance on 0·5 g. every 12 hours. The blood-sugar levels were reduced in all cases, the higher the initial fasting level the greater the hypoglycaemic effect produced. In 3 of these patients, when the drug was replaced by a dummy tablet relapse occurred after 3, 9 and 15 days respectively. Of the remaining 10 patients, 5 failed to respond. Four of them needed insulin to avoid ketosis. Supplementing the insulin by oral carbutamide gave better control but owing to the

fluctuations in the blood-sugar levels the effect of carbutamide was not statistically significant. Studies of arteriovenous blood-sugar differences and of changes in serum inorganic phosphorus levels provided no evidence that carbutamide increased the effectiveness of insulin. H. T. B.

**Carbutamide (BZ55) in Treatment of Diabetes.** I. Murray and I. Wang. (*Brit. med. J.*, 1956, **2**, 452.) Carbutamide was tried in a group of 23 diabetic patients who were over 45 years of age at the time of onset of the disease and who were of approximately ideal weight. 17 of them had never had insulin. No ketonuria was present at the start of the trial but it had been noted previously in 7 patients. Two young diabetics were also included in the trial. The patients were given dummy tablets for the first two weeks, and then tablets of carbutamide for two weeks. Dosage was an initial dose of 2·5 g. on the first day, then 1·5 g. on the second day and 1 g. daily thereafter. In 11 patients the mean blood-sugar level at noon was reduced to less than 180 mg./100 ml. and their glycosuria was markedly improved; they were regarded as successes. In 6 patients there was partial success, the glycosuria being markedly reduced but the blood-sugar level at noon remained above 180 mg./100 ml. There was no response in 6, all of whom had previously received insulin. The two young diabetics also failed to respond. Two patients did not respond while they were suffering from sepsis but gave a considerable response when the sepsis cleared. H. T. B.

**Carbutamide (BZ55) in Treatment of Diabetes.** G. Walker, W. L. B. Leese and J. D. N. Nabarro. (*Brit. med. J.*, 1956, **2**, 451.) Carbutamide was tried in 24 patients ranging in age from 38 to 82 years in whom diabetes had been recognised for from 1 to 42 years. Insulin had been given at some time to 10. All except 2 had glycosuria when carbutamide was started; 6 had mild diabetic symptoms and 5 had diabetic retinitis. None had ever had any significant degree of ketosis. Insulin was stopped in the case of patients receiving it; they were put on a low calorie diet and carbutamide was not started until the blood-sugar exceeded 200 mg./100 ml. Treatment was started with 2·5 g., followed by 1·5 g. the next day and usually 1 g. daily thereafter; it has been continued for 7 months in 2, 6 months in 4 and 3 or more months in most of the remainder. With 2 exceptions the blood-sugar levels are now satisfactory. Side effects included an irritant rash in 2 patients, making it necessary to stop treatment. One patient had a scaly eruption which disappeared in spite of continuing treatment. One patient developed mild hypothyroidism after treatment for 5 months with 1 g. daily; it responded to treatment with L-thyroxine. H. T. B.

**Catechol Amines in Lymph, Rate of Elimination of.** O. Celander and S. Mellander. (*Acta Physiol. scand.*, 1956, **37**, 84.) Lymph was collected from the thoracic duct of cats and man. Known amounts of adrenaline or noradrenaline were added to either heated or non-heated lymph or to Tyrode solution. The solutions were incubated at 38° between 0·5 and 4 hours; the pH of all the solutions being between 7·3 and 7·6. Assay of the catechol amines remaining after incubation was made on the isolated intestine of the rabbit. It was found that, in both cat and human lymph, the rate of destruction of adrenaline and noradrenaline was negligible in the untreated lymph. In denatured lymph there was some destruction but in Tyrode solution there was almost complete destruction after 2–3 hours. Results were similar for concentrations of adrenaline and noradrenaline varying between 1 and 10 $\mu$g./ml. This suggests that the catechol amines in some way combine reversibly with the protein molecules or radicals connected with these molecules and that the

free oxidation of the amines under such circumstances is largely inhibited. Denaturing the proteins by heating decreases but does not completely abolish the preserving capacity of lymph. M. M.

**CB1348 in the Treatment of Hodgkin's Disease.** B. A. Bouroncle, C. A. Doan, B. K. Wiseman and W. J. Frajola. (*Arch. int. Med.*, 1956, **97**, 703.) CB1348 is a nitrogen mustard derivative, *p*-bis-(2-chloroethyl)aminophenylbutyric acid, which has been shown capable of producing, when administered shortly after implantation, complete inhibition of the growth of the Walker rat tumour. It has also been found to inhibit particularly the lymphocytes of the peripheral blood of rats. This is a report on the treatment of 42 patients with CB1348; the patients included 24 with Hodgkin's disease, 10 with monocytic leukaemia, 3 with chronic lymphatic leukaemia, 1 with lymphosarcoma, 1 with acute lymphatic leukaemia, 1 with mycosis fungoides, and 1 with multiple myeloma. Of the 24 patients with Hodgkin's disease all were in an advanced stage of the disease with the exception of 4, and most of the patients had previously failed to respond to X-rays, nitrogen mustard or triethylenemelamine, or were unsuitable for the last two because of marked depression of the haemopoietic system. Excellent remissions were obtained in 6 patients with Hodgkin's disease, 1 with reticulum-cell sarcoma and 1 with monocytic leukaemia. Marked improvement was obtained in 9 patients with Hodgkin's disease. The initial dose of CB1348 in most patients was 0·3 mg./kg./day for a total period of 21 days, a second course being administered when symptoms of activity recurred. All patients after the second course, and most patients after the initial course were kept on a maintenance dosage of 0·05 mg./kg./day. Twenty patients received more than 0·5 g. of CB1348, the largest total dosage being 2·17 g. given over a period of 12 months. The compound was administered by mouth as 2 mg. tablets, given preferably before meals, 2 or 3 times daily. A few patients complained of nausea and anorexia, but insufficient to cause withdrawal of treatment. Several patients complained of nervousness. Most patients developed slight to moderate leucopenia, anaemia and thrombocytopenia, but at therapeutic doses the depressant effect on the bone marrow was only moderate and was rapidly reversible. The authors conclude that the compound is of value in the treatment of selected patients with Hodgkin's disease as a supplement to X-ray therapy. It has proved safer than TEM, and was preferred to nitrogen mustard in some cases, because it has few side-effects and is less damaging to the haemopoietic system. S. L. W.

**Cortisone Acetate in Chronic Asthma, Controlled Trial of Effects of.** Report to the Medical Research Council by the Subcommittee on Clinical Trials in Asthma. (*Lancet*, 1956, **271**, 798.) A trial of cortisone acetate was carried out at 6 centres on patients with chronic bronchial asthma who showed no evidence of severe broncho-pulmonary infection. One group of patients were given tablets of cortisone acetate and another group were given placebo tablets; the participating clinicians did not know which kind of tablets their patients were taking. Dosage of cortisone acetate was 300 mg. on the first day, 200 mg. on each of the next two days, and 100 mg. on each of the next four days. Thereafter dosage was adjusted to the patient's requirements. The daily dosage was given in 3 divided doses. 40 patients on cortisone and 37 on the placebo completed the course, which lasted 24 weeks. It was hoped to withdraw treatment during the subsequent follow-up period of 12 weeks but many patients in both treatment groups were still receiving tablets at the end of this period. There was unequivocal evidence of a slight advantage for the cortisone-treated patients as

regards physical signs and exercise tolerance from the 2nd to the 8th week of treatment. Thereafter in both respects the control group gained ground and at the end of the 24th week there was very little difference between the two groups. Cortisone showed no advantage in facilitating a return to work by those previously unable to work. Antispasmodic therapy was still needed. Two cortisone treated patients who did not complete the course withdrew from the trial because they developed status asthmaticus. Five of the placebo-treated developed status asthmaticus. 19 cortisone-treated and 15 placebo-treated patients wished to continue taking the tablets during the follow-up period. 36 cortisone-treated patients were followed for a further period of 6 to 12 months and, of these, 22 were still receiving cortisone; 12 of them were doing well. Of 14 patients not receiving cortisone, 7 were reported to be well. Side-effects during treatment were not serious. A psychoneurosis in one patient and a duodenal ulcer in two others may have been caused by or exacerbated by the treatment. In one patient the progress of tuberculosis of the kidney, discovered after 20 weeks treatment, may have accelerated. A few patients developed mild hypertension. In no case were the side-effects severe enough to cause any practical difficulties. H. T. B.

**2 : 5-Dimethyl-1 : 4-piperidyl Benzoate, Local Anaesthetic and other Pharmacological Properties of.** M. N. Gordin and G. I. Samarina. (*Izv. Akad. Nauk Kirg. SSR*, 136, *Ser. Fiziol. i Meditsinÿ*, 1954, **4**, 97–104; *Sovetskoe Med. Referat. Obozrenie*, 1956, No. 26, 129.) The effect of variations in the spatial configurations of the two methyl groups (*cis* and *trans*) and of the hydrogen atom and hydroxyl group on carbon (4) of 2 : 5-dimethyl-1 : 4-piperidyl benzoate is studied. Preparations A and B, differing only in the configuration of the hydroxyl group and the hydrogen atom in the 4-position, had about the same anaesthetic power as cocaine. Preparation C, in which the methyl groups of the piperidine ring are in the *cis* position, had a considerably greater anaesthetic effect and was more toxic than A or B. The following properties were common to all the preparations: the subcutaneous administration of aqueous solutions produced local anaesthesia; a fall in blood pressure followed subcutaneous or intravenous administration, except when B and C produced convulsions; a 1 : 1000 solution produced constriction of the posterior extremities of the frog; with more dilute solutions this effect was less marked and irregular; a 1 : 1000 solution lowered smooth-muscle tonus and caused temporary paralysis of the contractile activity of the isolated section of the small intestine of the rabbit. Because of their high toxicity, the preparations are unsuitable for injection. E. H.

**Hydroxyaluminium magnesium Aminoacetate, a New Antacid.** A. G. Zupko. (*J. Amer. pharm. Ass., Sci. Ed.*, 1956, **45**, 208.) Hydroxyaluminium magnesium aminoacetate ($C_2H_5O_4Al_3Mg,15H_2O$) is a white powder with a slightly sweet taste. It is almost insoluble in water and moderately soluble in dilute acids and alkalis. Solutions in acid rapidly form a heavy stable gel. The substance is non-toxic when tested in rats, and, when examined by the method of Hammarlund and Rising (*J. Amer. pharm. Ass., Sci. Ed.*, 1949, **38**, 586) it exhibits a long-sustained buffering action, the pH being maintained within the range 3·0 to 4·5 for 4½ hours, and does not stimulate the production of gastric acidity and acid rebound. It has little effect on the toxicity of the newer atropine-like agents (methantheline, methylhyoscine, propantheline, diphemanil, oxyphenonium and tricyclamol) in rats and affords partial protection against gastrointestinal ulceration to guinea pigs treated with antihistamine/depot histamine injections. It appears to be a suitable antacid for use in hyperacidity or peptic ulcer therapy. G. B.

**5-Hydroxytryptamine Creatinine Sulphate, Vasopressor Effect in Man.** S. I. Magalini, M. Stefanini and F. Smith. (*Proc. Soc. exp. Biol. N.Y.*, 1956, **92**, 433.) The vasopressor effect of 5-hydroxytryptamine creatinine sulphate (5-HT) was studied in 52 individuals who were either healthy or who were suffering from various diseases which were not associated with a high venous pressure. Intravenous injection of 0·3 μg./min. of 5-HT caused a transitory elevation of local venous pressure. Higher doses caused a greater rise of local venous pressure and, when administered in a short period of time, of arterial pressure. Elevation of the systemic venous pressure was not obtained even with extremely high doses of 5-HT. Intra-arterial administration caused a rise of pressure in the homolateral veins for 30 minutes or longer. Thus it is suggested that injected 5-HT is quickly removed from the circulation, perhaps by platelets or by other cellular elements retained in capillary beds and released slowly at a later time. M. M.

**Mecamylamine in the Treatment of Hypertension.** E. D. Freis and I. M. Wilson. (*Arch. int. Med.*, 1956, **97**, 551.) Mecamylamine (3-methylamino-*iso*camphane hydrochloride) is a ganglion-blocking agent which is well absorbed from the gastrointestinal tract. The hypotensive action following ingestion begins after 1 hour, reaches its lowest values in 2 hours, and disappears in 6 to 12 hours. In equipotent hypotensive doses mecamylamine did not produce as marked an inhibition of sympathetic vasoconstrictor reflexes as had been observed with hexamethonium. In 36 patients with severe hypertension treatment with mecamylamine in an average dose of 29 mg./day was followed by a mean reduction in blood pressure of 21 per cent systolic and 16 per cent diastolic in the supine position, and 27 per cent systolic and 20 per cent diastolic in the erect position. Continuous treatment for 1 to 4 months frequently resulted in improvement in the optic fundi and occasionally in the electrocardiographic patterns. A decrease in blood urea nitrogen levels occurred in patients exhibiting slight elevations but not in those with marked nitrogen retention. The side-effects were typical of those experienced with other ganglion-blocking agents, and included constipation, impaired visual accommodation, postural faintness, impotence, difficulty in micturition, and dryness of the mouth. Development of tolerance was slight or non-existent. The addition of small doses of hydrallazine appeared to produce a slight additional hypotensive effect in 3 of 13 patients, and reserpine seemed to produce an additional hypotensive effect in 5 of 11. Mecamylamine appears to offer a slight advantage over other ganglion-blocking agents in that the effective dose is much smaller and with careful dosage a more uniform reduction in blood pressure can be obtained. S. L. W.

**Mecamylamine, Pharmacology of.** R. V. Ford, J. C. Madison and J. H. Moyer. (*Amer. J. med. Sci.*, 1956, **232**, 129.) Mecamylamine is a ganglion-blocking agent with an action similar to that of hexamethonium and pentolinium. This paper presents observations of the pharmacological effects of mecamylamine in the experimental animal (dog) and in human hypertensive patients. The most important aspects of the drug are its long duration of action (average 17 hours), its prompt onset (average 68 minutes), and its complete absorption when administered orally. The average dose of mecamylamine required to produce significant effects in hypertension was 28 mg./24 hours, while with hexamethonium it was 2307 mg./24 hours, and with pentolinium 341 mg./24 hours. The percentage of patients achieving a responsive level was 90, 76 and 79 respectively (out of 81, 75 and 75 patients treated with each of the three drugs). The preference is for a three-dose-a-day treatment schedule, with the largest dose

given at noon. Side-effects include constipation, dry mouth, weakness and fatigue. Sympathomimetic drugs are effective in reversing hypotension due to mecamylamine. There is suppression of renal haemodynamics when the drug is administered in doses that produce marked reduction of blood pressure. It is considered that mecamylamine is the drug of choice in the treatment of moderate to severe hypertensive patients. S. L. W.

**Novobiocin, Clinical and Laboratory Studies of.** W. M. M. Kirby, D. G. Hudson and W. D. Noyes. (*Arch. int. Med.*, 1956, **98**, 1.) Staphylococci were shown to be remarkably sensitive to novobiocin *in vitro*, and there was no cross-resistance with other antibiotics. Pneumococci and Group A streptococci were inhibited by relatively low concentrations but are less sensitive than staphylococci. Among the Gram-negative organisms members of the *Proteus* group were shown to be moderately sensitive. An *in vitro* observation which might limit the clinical usefulness of the drug is that resistance of staphylococci develops rapidly and that the antibiotic is less active when there is an increase in the size of the inoculum of the bacteria. Of even more importance is the marked decrease in activity in the presence of serum; more than 90 per cent of novobiocin appears to be bound by serum proteins. Results of treatment with novobiocin in 75 patients with a variety of clinical infections were in general favourable, and appeared comparable to those obtained with erythromycin. In staphylococcal infections where prompt healing did not occur the infecting organisms rapidly became resistant to novobiocin. It is recommended therefore that novobiocin should be used exclusively for the treatment of infections caused by staphylococci resistant to other antibiotics. It is also recommended that novobiocin should be given in conjunction with another antibiotic to which the organism is sensitive in an attempt to prevent or delay the emergence of antibiotic-resistant staphylococci. S. L. W.

**Novobiocin Treatment of Pyodermas.** J. F. Mullins and C. J. Wilson. (*Antibiotic Med.*, 1956, **2**, 201.) Thirty patients with pyogenic infections of the skin were treated with novobiocin. Excellent results were observed in 24 cases, good results in 3, and failure in 3. Among the conditions successfully treated were impetiginised dermatitis, acute paronychia, furunculosis, ecthyma, and sycosis vulgaris; the failures occurred in one case of hidradenitis, and 2 cases of pustular bacterid. Infections caused by *M. pyogenes* var *aureus* and *Str. pyogenes* responded extremely well to dosages of 1·5 to 2 g./day administered by mouth. In the majority of cases the improvement was evident within 48 hours and the total treatment period usually ranged from 4 to 8 days. Lesions complicated by a Gram-negative organism responded poorly or not at all. No side reactions to the drug nor complicating candidiasis were observed. The authors conclude that novobiocin is as effective as the broad spectrum antibiotics in combating pyodermas due to *M. pyogenes* var *aureus* and *Str. pyogenes*. S. L. W.

**Phenoxymethylpenicillin Acid and Salt, Serum Concentrations of.** W. J. Kaipainen and P. Härkönen. (*Scand. J. clin. lab. Invest.*, 1956, **8**, 18.) A study of the blood levels of penicillin following the oral administration of phenoxymethylpenicillin acid and its potassium salt have shown that absorption was rapid and a high blood concentration was obtained in half an hour. The maximum level was reached in one hour and declined to a minimum after 4 hours. Higher blood levels were obtained when the penicillin was given on a fasting stomach than when administered after meals. The experiments were carried out on male and female bedridden patients and the dose was 300,000 units in tablet form. G. F. S.

**Whooping Cough, Vaccination Against: Relation Between Protection in Children and Results of Laboratory Tests.** Report to Medical Research Council. (*Brit. med. J.*, 1956, **2**, 454.) Two series of trials are reported. In the first, British vaccines were used, while the second series was planned to give information on the value of laboratory tests of vaccines and also to see whether British manufacturers could successfully use the manufacturing methods used by Michigan Department of Health which were known from previous trials to give much more effective products than those hitherto used in this country. In the first series 9 different vaccines were used, either plain suspensions or alum precipitated, and 9794 children aged 6 to 18 months completed the course of 3 injections. At least one-third of the children visited 24 to 48 hours after each injection with the plain suspension vaccines had no reaction either local or general; 3 had malaise severe enough to be kept in bed and 6 had screaming attacks. One severe reaction occurred in the group receiving alum precipitated vaccine after the third dose. Four children had convulsions within 72 hours after an injection. A total of 1325 cases of pertussis were diagnosed during a follow-up period of about 2 years. No striking differences in the protective power of the different vaccines were noted. Since vaccines were known to be of some value there were no control unvaccinated children but evidence from the home exposure rate suggested that all the vaccines were poor; of 547 exposed to home infection 379 (69 per cent) developed the disease. In the second series Michigan vaccine made from a culture of freshly isolated strains of *Haemophilus pertussis* in Bordet-Gengou medium was used as standard, and 3 British vaccines made by Michigan methods were tried together with a vaccine made by the State of New York Department of Health from a liquid culture of the same strain of *H. pertussis* as used in the Michigan vaccine. Eleven separate trials were made and 31,557 children completed the course of injections consisting of 3 doses each of 1 ml. Children visited after the first injection were also seen after the second and third injection, the total number of visits being nearly 10,500. Redness was noted in 6 per cent of visits and the children were "obviously disturbed by the tenderness" on 0·4 per cent of visits. 99 children had vomited once or more and 72 had other mild reactions. 8 children were recorded as having had convulsions within a period of 4 to 28 days. 34 developed paralytic poliomyelitis during the study; 3 who developed poliomyelitis within a month after an injection had paralysis only in the injected limb. Whooping-cough was subsequently diagnosed in 231 of the children. In some cases of home exposure chloramphenicol was used to treat the affected sibling with a view to shortening the duration of exposure to infection. The attack rate among 128 vaccinated children in such cases was 20 per cent whereas in 673 vaccinated children exposed to infection from siblings not treated with chloramphenicol the attack rate was only 13 per cent. No outstanding differences in the protective effects of the various vaccines were noted. The over-all attack rate in home exposures was 14 per cent whereas in previous trials the attack rate from home exposures in unvaccinated children was 87 per cent. Considerable protection was therefore afforded and the vaccine from the liquid culture was as good as that from cultures in solid media. In the laboratory test groups of 15 mice were immunised by intraperitoneal injection of graded doses of vaccine and challenged 10 to 14 days later by intracerebral injection of a challenging dose of *H. pertussis*. Some vaccines were tested for specific agglutinin production in mice and also in children. A correlation was found between the degree of protection in children and each of the laboratory tests but the mouse intracerebral challenge test is considered the most satisfactory. A freeze-dried British standard pertussis vaccine has been established and is thought to be stable.

H. T. B.