BRITISH PHARMACEUTICAL CONFERENCE NOTTINGHAM, 1952

(*continued from page 1000*)

REPORT OF A SYMPOSIUM ON RECENT DEVELOPMENTS IN THE PHARMACY OF ANTIBIOTICS

AT the Symposium Session the Chairman, Mr. H. B. Mackie, presided, and introductory addresses were given by Mr. W. A. Woodard, Mr. W. Trillwood and Mr. J. O. Davidson.

Mr. W. A. WOODARD read, in abstract, a communication dealing with recent developments in the pharmacy of penicillin, streptomycin and dihydrostreptomycin, chloramphenicol, aureomycin and terramycin (*see Review Article, pages* 1009 to 1036).

Mr. W. TRILLWOOD, dealing with the subject from the point of hospital practice, said:—Although a great deal of knowledge is available to the physician, surgeon and pharmacist by the time a new antibiotic is issued for use in hospital, many new problems confront the hospital pharmacist as clinical investigation proceeds and new uses are suggested. Whatever the problem, the pharmacist augments his efforts with the accumulated experience of all whose skill is at the disposal of the hospital service.

Penicillin should be kept cool, dry and sterile—the condition in which it is supplied by the manufacturer. To ensure maximum potency at the time of injection it should be dispensed as it is received in its original container as a dry sterile powder, and the procedure is to supply with the dry powder a sterile solvent and sterile injection apparatus. The pharmacist should provide a sterile syringe service, so that each injection is given with a clean, dry, sterile syringe and a clean, dry, sharp, sterile needle. For intrathecal injections a solution containing a precise concentration of the antibiotic is required, and this must be prepared by the pharmacist. Storage at a low temperature must be ensured by careful labelling, by the regular inspection of ward stocks, and by the withdrawal of out-dated material.

The increasing emergence of penicillin-resistant bacteria had occasioned much discussion. In Oxford, the dosage technique had gone the full circle. With very few minor exceptions no delay-penicillin is used. Instead, penicillin B.P. in high dosage (500,000 I.U.) is given in acute infections, at twelve-hourly intervals; thus providing a germicidal concentration to a wider range of strains of bacteria than procaine penicillin, intermittently it is true; yet it is believed that intermittent bactericidal levels of penicillin are likely to be more effective than continuous bacteriostatic levels.

In view of the increased emergence of insensitive organisms, and the widening bacterial range of antibiotics, sensitivity tests had assumed an

added importance. In requesting sensitivity tests, the physician wants to know what organisms are present, what is the antibiotic of choice, and what is the degree of sensitivity. Bacteriological skill beyond the scope of the pharmacist was required to name and type bacteria; the degree of sensitivity might then be determined by a technician. Sensitivity to penicillin is usually expressed as the concentration of penicillin, in I.U./ml., required to inhibit the organism tested. The question is often posed: an organism has a sensitivity of 0·01, 0·1, 1, 10 or 100 I.U. of penicillin, what dosage of penicillin should be given intramuscularly? The properties of penicillin provide the answer: penicillin is rapidly absorbed and rapidly excreted, blood levels of 10 I.U./ml. are rarely reached. The precise degree of sensitivity is of theoretical interest only; for practical purposes the organisms should be reported simply as "sensitive" for those with a sensitivity below 10 I.U./ml. or "insensitive" where the sensitivity is above 10 I.U./ml.

Bacterial resistance to antibiotics is an ever-present source of anxiety, and many promising new agents have been discarded as organisms have become resistant. It seemed that streptomycin was likely to be short-lived, but, fortunately, the collateral use of *p*-aminosalicylic acid prevents or delays the tubercle bacillus from developing streptomycin-resistance. Unlike penicillin, streptomycin has not been required in diverse pharmaceutical forms. Apart from intramuscular and intrathecal injections and the use of solutions for application to septic granulation areas in plastic surgery, the use of streptomycin is limited. Streptomycin is far more stable than penicillin and does not require any special precautions other than those normally required for the preparation of sterile material. Administration by injection has disadvantages; the injection may be painful, and even when painless, most patients, particularly children, are apprehensive of injections. There has been a general desire for agents which are effective by the oral route, and chloramphenicol, aureomycin and terramycin fulfil this requirement. In addition, these new agents have increased considerably the effective clinical range of antibiotics, notably in providing the first effective weapons for virus and rickettsial infections.

Chloramphenicol is now in general use and is freely available. The use of aureomycin and terramycin is restricted to hospitals, except for certain specified clinical conditions for which general practitioners may obtain supplies through the regional distribution centres.

The shift from antibiotics given parenterally to those effective by mouth is not an unmixed blessing. The rapid absorption, circulation and excretion of penicillin has not resulted in the elimination of the normal bacterial flora of the intestinal tract. This has happened, however, with the oral antibiotics. Not only does the sterilisation of the gut necessitate supplementary administration of vitamin B complex, but a still more disturbing condition may arise. With the sterilisation of both pathogenic and benign organisms, the field seems to be clear for fungal infections, and already deaths have been reported from yeast and monilia infections following the use of oral antibiotics. As the oral antibiotics become more widely used, the demand for fungicidal drugs will increase.

He concluded with an acknowledgment to Dr. R. L. Vollum, Director of the Public Health Laboratories, Oxford, for permission to publish his sensitivity table of antibiotics.

ANTIBIOTICS
Table of Sensitivities

Organism	Penicillin	Streptomycin	Aureomycin	Chloram-phenicol	Terramycin
β-hæmolytic streptococcus	++++ 0·001 to 0·2*	+++ 0·5 to 120*	+++ 0·3 to 2·5*	++ 0·3 to 2·5*	++? 1·0 to 1·5*
α-hæmolytic streptococcus	++++ 0·05 to 5	+++ 2·5 to 120	+++ 0·3 to 2·5	?	+? 0·3 to 2·5
Pneumococcus	++++ 0·001 to 0·2	+++	++ 0·1 to 0·3		++? 0·02 to 2·5
Staphylococcus aureus	++++ 0·002 to 1000	++ 3·50	++++ 0·2 to 5	+ 1·5	++? 0·5 to 1·5
Neisseria	++++ 0·002 to 0·3	++ 5·40	++	+	+? 0·2 to 2·5
Clostridium welchii	++++ 0·1 to 1	–	?	?	?
Hæmophilus influenzæ	– 0·2 to 10	+++ 1 to 50	+++ 1 to 5	++ 0·6	+? 2·5 to 4·0
Hæmophilus pertussis	–	–	+?	++ 0·2 to 0·3	? 5·0
Brucella	–	–	++++ 0·75	++++	++? 0·3 to 2·0
Bacterium coli	–	+++ 0·3 to 1000	+++ 5·0	+++ 3 to 10	++ 2·0 to 5·0
Salmonella typhi	–	–	+	++++ 5	?
Shigella	–	–	+++	+++ 1	?
Proteus	–	+ 1 to 1000	+ 2·5 to 100	+ 10 to 100	+? 50
Pseudomonas pyocyanea	–	++ 2 to 1000	– 10 to 50	– 3 to 100	+? 25
Mycobacterium tuberculosis	–	++++ 0·1 to 1	–	–	–
Rickettsia	–	–	+++	+++	++?
Leptospira	+	–	?	?	?
Treponema pallida	+++	?	+	+	+
Administration	Parenteral	Parenteral	Oral	Oral	Oral
Optimum *pH*	5·5 to 7	7·4 to 9	4 to 5	2 to 9	4 to 7
Toxic effects	Dermatitis	Dermatitis Vertigo Deafness B. deficiency	Nausea Diarrhœa Stomatitis B. deficiency	Nausea Diarrhœa Stomatitis B. deficiency	Nausea Diarrhœa Stomatitis B. deficiency

++++ Probably most effective treatment.
+++ Satisfactory.
++ Moderately satisfactory.
+ Possibly effective.
+? Preliminary reports satisfactory.
– No effect.
? Unknown.

* In vitro sensitivity: In units/ml. for penicillin and in μg./ml. for other antibiotics.

Mr. J. O. DAVIDSON, speaking from the point of view of general pharmaceutical practice, said:—Although our connection with antibiotics is limited to penicillin, streptomycin and chloramphenicol, a large number of preparations of these three substances exists. We have, therefore, to be

prepared to meet a demand quite different from that in the specialised field of the hospital service.

Penicillin occurs in several closely related forms, of which the best known and most important is benzylpenicillin, the soluble sodium salt being the form most frequently met with in general practice.

The preparations most frequently required are:—

Aqueous Injection: Initially, penicillin was injected as a sterile, aqueous solution of from 20,000 to 30,000 I.U./ml. at intervals of from 3 to 4 hours over a 5-day period. The concentration was later increased to 200,000 I.U./ml. and, on occasion, 500,000 I.U. in 2 ml. has been administered at from 4 to 12-hourly intervals. *Oily Injection:* To avoid the dosage frequency of the aqueous solution, oily injection of penicillin B.P., at a concentration of 300,000 I.U./ml. was introduced. Although its high viscosity and liability to cause irritation tend to reduce its popularity, it is still favoured by some practitioners. *Procaine Penicillin:* This is a sparingly soluble salt which is suspended in sterile water before use at a concentration of 300,000 I.U./ml. The suspension retains its potency over relatively long periods. *Fortified Procaine Penicillin* contains 300,000 I.U. with the addition of 100,000 I.U. of benzylpenicillin. *Other Suspension Injections:* Many other suspension injections are available for special conditions. Chief among them is a hydriodide ester which produces a relatively high concentration in the lungs. Another preparation reduces the administration frequency to 24- and even 48-hour intervals. *Tablets:* Penicillin tablets, administered orally when injections are undesirable, usually contain from 100,000 to 200,000 I.U. This is wasteful and expensive, as 5 times the injectable dose must usually be given. *Lozenges, Gums:* A mixture of hard and soft white paraffin, after suitable heat treatment and when sweetened with soluble saccharin and flavoured with oil of peppermint, gives a satisfactory chewing material in which to incorporate penicillin. *Eye-drops:* Penicillin eye-drops, normally containing 15,000 I.U. in 110 minims, should be stored in a cool place and used within 7 days. *Insufflation:* An aural insufflation containing 5000 I.U./g. in sterile sulphathiazole is frequently required for use in a Cade's insufflator. *Oily Nasal Drops:* These are also prescribed at a concentration of 5000 I.U./ml., prepared by dissolving the penicillin in a small amount of distilled water, adding 1 per cent. of phenoxetol as a preservative and making up to volume with Eucerin oil. *Creams, Cones, Dressings, Ointment, Pessaries:* Most of these are now available commercially.

Streptomycin is used either as the hydrochloride or the sulphate or as a double salt formed with calcium chloride. Dihydrostreptomycin B.P., which is formed by the reduction of streptomycin, is used as the hydrochloride or as the sulphate. Its properties, antibacterial activity and therapeutic efficiency, are similar to those of streptomycin and it was thought for a time that this modification considerably reduced the toxicity of the drug. These two substances differ chemically and are not interchangeable.

The preparations most frequently required are:—

Aqueous Injection: A sterile aqueous solution of streptomycin-calcium

chloride complex is most frequently required, the usual strength being either 0·5 g. in 2 ml. or 1·0 g. in 5 ml. It is given intramuscularly in the treatment of tuberculosis, either alone or simultaneously with *p*-amino-salicylic acid. *Eye-drops:* 10 mg./ml. of sterile normal saline. *Eye-ointments:* 0·5 per cent. in sterile eye ointment base. *Solution or Powder for Wounds or Ulcers:* 5 per cent. solution, or 5 to 10 per cent. powder in sterile sulphadiazine. *Cream:* 5 per cent. in a base similar to that used for penicillin cream. *Pessaries:* 100 mg. of streptomycin with 50,000 I.U. of penicillin in oil of theobroma. The streptomycin must be finely powdered to avoid the possibility of small crystals gravitating to the points of the pessaries before they set.

Chloramphenicol occurs as whitish crystals having a very bitter taste. It is only slightly soluble in water but dissolves readily in ethanol and in propylene glycol giving stable solutions. It is absorbed well after administration by the mouth. It is given in the following forms:— *Capsules:* Hard capsules each containing 250 mg., the recommended daily doses being 30 mg., 75 mg., or 100 mg./kg. bodyweight in suitably divided doses. *Palmitate Suspension* for infants and children unable to swallow capsules. This non-bitter derivative hydrolyses in the small intestine, liberating chloramphenicol. Two teaspoonfuls are equal to one 250-mg. capsule. *Suppositories* each containing 125 mg. in cocoa butter. *Eye-drops:* either a 0·25 per cent. solution (saturated) or a 0·5 per cent. borate buffered solution of the drug. *Eye-ointment:* 1 per cent. in oculentum base. *Cream:* 1 per cent. in hydrous emulsifying ointment. *Dusting Powders:* 2 to 3 per cent. in dried sterile lactose. *Ear-drops:* 10 per cent. in propylene glycol. *Use in Dentistry:* Recently, a suspension of 1 g. each of chloramphenicol, streptomycin and sodium caprylate with 3 ml. of propylene glycol has been required for insertion into inflammatory root areas of teeth via the root canal. The function of sodium caprylate is to inhibit the action of the yeasts which are unaffected by the antibiotics.

Mr. H. A. TURNER (Nottingham) observed that the subject of antibiotics, which began in the academic field, had now passed into the hands of manufacturers. The B.P. statement that benzylpenicillin was so stable that when heated in an open vial at 100° C. for four days it lost not more than 10 per cent. of its potency spoke well for the quality of the material now available.

Mr. A. F. CALDWELL (Singapore) said that temperatures should be stated more precisely than by the word "normal." This was of importance to workers in tropical countries. With regard to the oral use of antibiotics, in Singapore trouble had been experienced with monilia and fungus infections. There was also the problem of allergic sensitivity, especially in patients using penicillin lozenges.

Mr. A. STERLING (London) said that the length of treatment with antibiotics and the cost were important in hospital practice. No mention had been made of drugs which delayed excretion of the antibiotics. For instance, was there any substance which was not toxic to the kidney and which would delay excretion of penicillin?

Mr. J. M. MYERS (Bradford) asked Mr. Woodard whether there was a

suitable solvent for aureomycin in 2 to 3 per cent. solution for topical application. Was there any evidence that chloramphenicol and aureomycin were inactivated by specific enzymes in the way that penicillin was inactivated by penicillinase? He asked for information regarding staff, cost and type of syringe required for the maintenance of a sterile syringe service for a 500-bed hospital. Was a mixture of chloramphenicol and streptomycin efficacious for sterilising root canals, and was it good practice to continue the use of antibiotics in dentistry, because of sensitisation resulting from continued local application?

Mr. P. CLAPHAM (Speke) said he understood that "tweens" were normally used in preparing aqueous injections, and inquired whether they could be used for oily injections? Four days seemed a short period for the storage of buffered penicillin solutions. Advances were taking place in which higher concentrations of soluble penicillin added to procaine penicillin were made available. There was room for the development of injections which enabled higher doses of soluble penicillin to be given with the usually accepted doses of procaine penicillin. This would achieve a bacteriostatic level of soluble penicillin, and would maintain a suitable blood level over a period, thus reducing the number of injections. Generally, sodium carboxymethylcellulose was used in very small quantities, and if the grade was carefully selected it was a very useful addition. There were improved forms available which produced an almost clear solution.

Mr. J. H. OAKLEY (London), referring to the improved ointment base in the B.P. Addendum 1951, gave figures showing the improvement in stability using potassium benzylpenicillin. A 5 per cent. loss of potency occurred in 12 months when the ointment was stored at 5° C., at 20° to 28° C., or at 35° C. Lozenges were now so stable that there was no significant loss in twelve months at the above temperatures, provided they were kept dry. With solution-tablets there was a 10 per cent. loss of potency in 12 months. Here, most of the losses occurred just after manufacture, but if the tablets were buffered there was no loss of potency after 8 months. It was a pity that the eye ointment of penicillin was not changed at the same time as the ointment.

Mr. T. D. WHITTET (London) said that since the introduction of penicillin in lactose for topical application the use of sulphonamides as diluents in powders had, in general, been abandoned at his hospital. Streptomycin with maphenide had been used topically, and sulphacetamide with penicillin powder had been useful for infected root canals. In making potassium benzylpenicillin with lactose powder a loss of potency of 40 to 50 per cent. was obtained using dry heat at 150° C. even when the lactose had been previously dried. Chloramphenicol could be sterilised by dry heat at 150° C. for one hour. An intrathecal injection of chloramphenicol containing 2·5 mg./ml. could be sterilised by autoclaving.

Mr. F. H. OLIVER (Sunderland) said that the determination of the sensitivity of the organism to the antibiotic would lead to a saving in the antibiotics and would prevent their misuse. In his view the determination of the sensitivity of organisms was an excellent example of pharmacy as

opposed to dispensing, to which the pharmacist could make a valuable contribution.

Mr. J. C. HANBURY (Ware) said it was clear that the dangers inherent in the use of the newer antibiotics were so serious that the continued use of penicillin, with its lower toxicity, was called for. In his view more discrimination was needed in the use of ointments, creams and lozenges of penicillin in local infections. The pharmacist should familiarise himself with the use and abuse of antibiotics.

Mr. R. L. STEPHENS (Brighton) suggested that the stability of penicillin oral tablets and lozenges would be improved by replacing the cottonwool packings with plastic or nylon. Nylon yarn had a water absorption of under 1 per cent., whereas cotton wool normally absorbed about 8 per cent. of moisture, which must adversely affect the storage life of the tablets. At the same time the use of a coloured silica gel moisture indicator might be of advantage. Had Mr. Woodard any experience of the combination of two or more antibiotics in one preparation or of their simultaneous use? In particular, the combination of streptomycin and penicillin was very popular with ships' doctors, and he asked why more of it had not been seen in this country.

Mr. E. MATTHEWS (Portsmouth) said that in cases of shock it was necessary, in order to get absorption, either to use intra-arterial injection or to add a spreading agent, such as hyaluronidase, and he asked for information on the formulation of such injections. Was anything known of the formulation of antibiotics with an antihistamine, and would it be pharmacologically sensible as a means of preventing anaphylactic emergencies?

Mr. D. M. BRYCE (Barnet) asked Mr. Woodard what was his experience of sodium carboxymethylcellulose, and whether he was aware of any tissue damage following injection.

Mr. W. P. LEGGETT (Speke) referred to the co-operative work on bacteriostatics which was going on in the laboratories of penicillin manufacturers and others interested. The papers suggested a return to the use of soluble penicillin salts and it might be that developments towards improvements in buffering would follow. Most of the bacteriostatics tried had failed owing to incompatibility. They had turned, therefore, to the newer agents, such as the esters of *p*-hydroxybenzoic acid and the quaternary ammonium compounds. These were compatible, and the former were quite effective against *Pseudomonas pyocyanea*, though they did not suppress certain resistant strains of staphylococci: the latter, on the other hand, "almost fertilised" *Ps. pyocyanea*.

Mr. J. R. ELLIOT (London) said that at his hospital it had been found possible to reduce the concentration of aureomycin in ointments from 3 to 1 per cent. and obtain similar clinical results. Why did Mr. Trillwood prefer penicillin as a dry powder to a ready-made injection issued from the pharmacy? Multiple dose containers holding 5 to 10 mega-units of penicillin had been found useful so that supplies would be used up within the stated pharmacopœial life. Injections in multiple dose containers were cheaper and easier to prepare.

Mr. A. MARSH (Brighton) stated that sensitivity tests were part of the duties of the pharmacist, because not every hospital had the services of a bacteriologist or laboratory technician. He agreed with Mr. Hanbury that the pharmacist should know all the properties of the antibiotics, including how to test for sensitivity.

Mr. R. W. GILLHAM (Leeds) referred to some unusual preparations, including a mixture of penicillin with blood plasma, penicillin tampons, penicillin with talc, and dihydrostreptomycin as a bulk injection of 50 ml. containing 1 g./ml. with a dose of 0·5 ml. for a child; this gave a solution of treacly consistency.

Dr. E. I. SHORT (Beckenham) said sensitivity tests acted as a control on excessive prescribing of antibiotics. Had Mr. Trillwood any experimental or clinical evidence to support his belief that intermittent bactericidal levels of penicillin were more effective than continuous bacteriostatic levels?

Mr. H. WILLIAMS (Reading) said that in his experience general practitioners were tending to prescribe mixtures containing penicillin in preference to injections. Could Mr. Davidson suggest the best solvent and say how he would dispense such a preparation?

Mr. N. A. HERDMAN (Speke) said that leading dermatologists were not in favour of topical penicillin preparations. The variation in the views of doctors on such treatment led him to suggest that the collection and correlation of medical information might be the subject of a future symposium.

Mr. S. POWLSON (London) queried the statement that chloramphenicol could be sterilised at 150° C. The suppliers of the drug suggested that a suitable method of sterilisation was to heat the chloramphenicol in fine powder at 105° C. for one hour. That had been issued as a suspension in water at a strength of 1 or 2 g. in 10 ml. for injection into the pleural cavity. Aureomycin was being used in concentrated solution as an ærosol.

Mr. C. W. ROBINSON (Liverpool) said that a number of different brands of penicillin lozenges described as "B.P." contained added colour and flavour. It would be of advantage for the Pharmacopœia to lay down standards.

Miss I. HARRIS (Bromley) pointed out that penicillin and chloramphenicol were frequently prescribed to be administered together and asked whether the simultaneous administration of penicillin and other antibiotics was advantageous.

Mr. D. F. SMITH (Bournemouth) said that he had used with success polyvinylpyrrolidine in preparing a chloramphenicol suspension for introduction into the pleural cavity. With regard to therapy with two or more antibiotics, American workers had found that while penicillin and streptomycin could be administered concurrently and with complementary effects, penicillin or streptomycin was antagonistic to other antibiotics, such as chloramphenicol or aureomycin.

Mr. H. TREVES BROWN said that Mr. Trillwood referred to the use of vitamin B complex tablets to mitigate the effects of antibiotics when administered orally. It would be interesting to know whether the view

was still held that they had some effect. Their use started when the occurrence of black tongue was reported and somebody found that nicotinamide and nicotinic acid cured it. Then it was suggested that as the condition occurred suddenly, it could not be a vitamin deficiency, and he understood that the prevailing view was that the vitamin B complex was not a cure for the symptoms following oral treatment with antibiotics.

Mr. F. G. WELLS (London) said he wondered if it was realised how seldom the retail pharmacist had an opportunity to use his knowledge of antibiotics, and how the medical man would receive any attempts to tell him how to prescribe? The main worry in retail work was the present multiplicity of preparations on the market. The use of proprietary names necessitated the stocking of more than one brand of an antibiotic preparation, and the matter was not being viewed from the pharmaceutical, but rather from the commercial, point of view.

Mr. J. JACOBS (Sunderland) referred to tyrothricin and bacitracin, which were used topically. More information on these was desirable.

Mr. J. O. DAVIDSON, in reply, said that in the use of suspensions in dentistry, the aim was to stop the formation of chronic ulcers in the root area. Mr. Clapham's remarks concerning procaine penicillin and his defence of it as an injection were interesting. The fact that the oily injection of penicillin was going out of use was rather surprising, because it seemed much more logical to inject a little oil rather than procaine. Lozenges were being used very widely for all purposes, but the sterile cream was falling out of favour. It was not his experience that the injection of penicillin was giving place to oral administration in mixtures. In his opinion an aqueous solvent was the best for penicillin.

Mr. W. A. WOODARD, in reply, agreed that it was important to specify temperature. In preparing oily suspensions "tweens" and similar preparations had been used with partial success. Aluminium stearate gave a permanently stable suspension when the preparation was properly formulated and prepared. Plastic materials were coming into use for the protection of tablets in place of cotton wool. Combinations of streptomycin and penicillin were extensively used in the United States. Because of the wider spectrum effect such combinations were active against Gram-negative and Gram-positive organisms, and were clinically more effective. Incorporation of soluble forms of penicillin reduced their stability in procaine penicillin preparations. Much depended on the degree of substitution in sodium carboxymethylcellulose. It was reasonably safe material, provided it was used in small amounts, and the correct grade chosen. The only way of determining whether a grade was suitable was by animal tests and clinical trials. Agreeing with Mr. Leggett, bacteriostatics in the suspension type of product could frequently give rise to more trouble than in penicillin solutions. Bacteriostatics were often not compatible with added suspending and wetting agents. He did not consider that the B.P. went far enough in the control of penicillin lozenges and other preparations of that type.

Mr. W. TRILLWOOD, in reply, said that he had no experimental evidence to offer with regard to the desirability of having intermittent bactericidal

levels of penicillin rather than continuous bacteriostatic levels. However, work was being done at Oxford because there was evidence that in a number of hospitals something like 30 to 35 per cent. of all septic cases had resistant organisms. It was felt that that had largely been caused by under-dosage with penicillin. It was also thought that it might have been caused by the use of delayed action penicillin giving a long continuous bacteriostatic level. Penicillin in the right dosage was a bactericide and should be used as such. It was impossible for the general practitioner, and difficult for the nursing staff, to administer injections three-hourly in order to maintain a continuous bactericidal level; but there was a school of thought which took the view that it was a good thing to let penicillin completely disappear from the blood for a period. The best time to strike bacteria was when they were in an active state of metabolism. With regard to the cost of treatment with antibiotics, 30 drugs accounted for two-thirds of the hospital drug bill and the five substances: penicillin, streptomycin, chloramphenicol, aureomycin and *p*-aminosalicylic acid accounted for 50 per cent. A sterile syringe service would always be expensive. A saving could be made in the avoidance of breakages by the use of skilled technicians In his own case the breakage rate was less than $\frac{1}{2}$ per cent. The case for sensitivity tests had been stated in the paper. If a mixed culture were being investigated the doctor would want to know what organisms were present, and what was the antibiotic of choice. In his experience local applications of penicillin or antibiotics were not used to any great extent. Streptomycin was used in plastic surgery. He believed in keeping penicillin powder dry because a sterile syringe service was provided which was essential quite apart from antibiotics. Hospital pharmacists knew that ward stock should be regularly turned over to ensure that solutions of penicillin would not be inactive when administered to the patient but could they always be sure that this was done? With the dry powder, and by allowing the nursing staff to add sterile water with sterile apparatus, as much as possible had been done to ensure that the patient received a penicillin injection of the strength which the prescriber ordered. He was unable to answer the point raised by Mr. Treves Brown.