# REPORT OF A SYMPOSIUM ON PHARMACEUTICAL FORMULATION

At the Symposium Session the Chairman, Professor H. Berry, presided and Mr. C. J. Eastland read a paper on "Some Aspects of Modern Formulation." Introductory addresses were also given by Mr. W. Nixon, Mr. W. Swallow and Mr. Donald W. Hudson.

## Some Aspects of Modern Formulation

By C. J. Eastland

Gaddum[1] has stated that "the successful use of drugs depends upon maintaining an adequate concentration at the site of action for an adequate time, and the achievement of this aim depends on the method of administration, the frequency of administration, and the use of the preparation dispensed in an appropriate form." The fulfilment of the last requirement implies successful formulation.

The subject of formulæ was dealt with briefly by the opening speaker of the Symposium at last year's Conference, and in his paper Todd[2] defined formulation as "the art of presenting a substance in a form in which it best exhibits its characteristic properties." A good formula, therefore, results in a product which is safe in use, within the prescribed dose range, convenient in application by physician and patient, and which is, so far as possible, what is termed "pharmaceutically elegant." It is essential, also, that the product should retain its properties for a reasonable period of time, and in some cases be able to withstand extremes of temperature*.

These criteria, therefore, will be the terms of reference for this Symposium.

Comparing formulation of the old type with that of the present day, Professor Todd was perhaps a little pessimistic when he said "there now seemed to be little left for the pharmacist to do, but to dissolve complex organic chemicals in sterile water." As a matter of fact, a survey made in the U.S.A. in 1947 disclosed that over 54 per cent. of the drugs then in use had been wholly unknown 10 years before. Since then the output of new remedies has certainly shown no sign of slackening; and even to make sure that the comparatively simple procedure of dissolving a given substance in sterile water is the best method of presenting a drug has surely called for experimental work by some pharmacist in his rôle of formulator. Chemists are sometimes too optimistic with regard to the stability of their newly synthesised compounds, and

* Other abnormal climatic conditions can usually be met by the package form, a consideration of which is beyond the present brief. However, a formula must sometimes be adapted to the availability of packing material and containers. During the war, when pure tin collapsible tubes were unobtainable and had to be replaced with tubes of sometimes imperfectly tinned lead, much trouble was experienced with preparations containing sodium alginate. What was intended to be a salve-like product was soon converted into a gel owing to the formation of lead alginate.

it is the pharmacist in his effort to produce, say, an injectable form of a new drug, who may discover loss on sterilisation by heat of the solution —or even by adsorption on the sterilising filter pad! Such losses do quite frequently occur when the concentration of the drug is of a low order or when the solution is unbuffered. It is the pharmacist, also, who must determine the optimum *p*H value, having regard both to the effective life of the drug and to the comfort of the patient when receiving the injection. The pharmacist, too, must consider whether a relatively transitory effect is required or a prolonged action: if the latter, he must decide what must be done to maintain an effective concentration in the blood and tissues. To provide the right answers to such problems is certainly a challenge to the pharmacist's knowledge, skill and ingenuity.

## Modern Trend in Formulation

Perhaps the most outstanding features of modern formulation are simplicity and specificity; each ingredient must fulfil a well-defined function. Gone are the days of " blunderbuss " formulation, which depended upon the empirical method of trial and error, and which appears to have been devised to suppress as many symptoms as possible without regard to the removal of the causes of those symptoms. The famous Theriacæ of the fifteenth and sixteenth centuries, containing in some cases literally hundreds of ingredients, were avowed attempts to meet all contingencies—probably a wise precaution in the days of the Borgias!

Certain modern formulæ, such as those used by the microbiologist for the nutrition of his test organisms, may appear to emulate the worst efforts of polypharmacy; but to these, as also to many of the modern medicinal formulæ, it is perhaps more appropriate to apply the term " barrage "[3]. The " barrage " formula does at least aim its several shots scientifically—at the one target! It is recognised, for example, that the complementary and synergistic action of a mixture of the individual members of the vitamin B complex, when administered in correctly balanced proportions, gives the best results in the prolonged treatment of disorders due to vitamin B deficiency.

Again, the administration of a combination of sulpha drugs such as a mixture of sulphadiazine, sulphamerazine and sulphathiazole, is a means of avoiding precipitation of the individual sulpha drugs in crystalline form in the renal tubules, the combination possessing the valuable property of being more soluble in urine than the equivalent of any one of these drugs alone. Then, again, there is the combination of sulphathiazole and penicillin and the use of mixtures of antibiotics to widen the bacteriological " spectrum." Recently, too, there has been the employment of streptomycin with *p*-aminosalicylic acid which has proved particularly effective against tuberculosis. Although this last example is not, strictly speaking, one of formulation since the two drugs are not given in one preparation, it is cited as a good case of synergistic action, each drug acting through a different mechanism to achieve a common

therapeutic aim. The use of *p*-aminosalicylic acid, moreover, makes it possible to administer lower doses of the streptomycin, thus reducing the risk of the toxic symptoms hither to associated with this antibiotic.

*Combined Operation:* Scientific formulation may be regarded as the last phase in a "combined operation," with the chemist, biochemist, bacteriologist, pharmacologist, pharmacist and clinician all taking part, and frequently, but not necessarily, in that order. The particular method of formulation of a new drug can produce unexpected results, and a new preparation should always be submitted to the pharmacologist before it is handed over to the clinician for use on the human.

Of the many changes—apart from the decreasing use of the old galenical preparations—which have taken place in pharmacy during the past two decades, the most outstanding have been: the great increase in the parenteral administration of drugs; the transition from pills to tablets; and the scientific study and development of new bases for the production of ointments and creams. The main theme of this contribution to the Symposium is a consideration of the different methods which have been adopted for the prolongation of the action of drugs and particularly of those intended for intramuscular or subcutaneous administration.

## Formulation: With Special Reference to Depot Therapy

During the past 20 years or so, control of rate of liberation of a drug from the "pool" at the site of injection has received ever-increasing attention, especially since the discovery that the initially scarce and costly drug, penicillin, was rapidly eliminated after injection by the intravenous route.

In the great majority of cases, the aim is to decrease the rate of liberation in such a way as to maintain an effective concentration of the drug in the blood plasma over a conveniently long period with the minimum number of injections. The chief factors determining the rate of absorption from a given intramuscular or subcutaneous injection are: (a) The site of the injection, (b) The local circulation, (c) The solubility relationships between the drug, the solvent and the tissue fluid, (d) The surface area of the depot.

These factors will now be dealt with in turn:

(a) From the point of view of formulation, there is little to be said concerning the site of the injection, apart from the fact that it is generally accepted that intramuscular injections are absorbed more quickly than subcutaneous injections.

(b) The rate of absorption of a drug from a depot depends upon such factors as the local blood circulation through the injected area, the spreading effect of the massage, and the diffusion gradient of the drug between the injection vehicle and the intracellular fluid. Absorption will be accelerated by local application of heat, owing to dilatation of the blood vessels; and will be correspondingly retarded by the local application of ice[4]. What may be regarded as a special form of depot therapy is the

now well-known and officially recognised use of adrenaline and other vasoconstrictor drugs in conjunction with local anæsthetics. The impairment of the blood flow from the area around the injected mass reduces diffusion and restricts the analgesic effect to a limited area.

(c) Generally speaking, after allowing for the nature of the solvent or vehicle in which it is presented, the more water-soluble the drug, the more rapidly is it absorbed. The obvious method, therefore, of prolonging a drug's action is to convert it into a less soluble salt, ester or complex, and to inject this either as a suspension, or as a solution in a suitable solvent from which it will then be precipitated, at the site of injection, when it comes into contact with the tissue fluids. Thus penicillin, for example, can be converted into a number of more or less insoluble salts such as those of silver, iron, copper and aluminium; although none of these except the aluminium compound has been used clinically. In mice, Reid[5] found that the aluminium penicillin in oil was more effective than the sodium or calcium salt in an oil and beeswax mixture. More recently[6] it has been reported that the response to the oral administration of aluminium penicillin was entirely satisfactory.

Esterification of steroids, by altering their partition between oil and water in favour of the former, tends to slow down the release of the active substances from the injection site. Moreover, in addition to a more prolonged action, these steroid esters appear to have an increased therapeutic efficacy. This effect is well marked in the case of cortical hormones, as for example deoxycortone acetate[7], and is also shown by œstradiol benzoate[8] and testosterone cyclopentylpropionate (in rats)[9].

The prolonged action here is probably due in part to the ester group having first to be removed before the specific action of the steroid can be manifested. The side chain may also delay the inactivation of the compound by the liver.

Combination with protein is another method of converting a drug into an actually or potentially less soluble derivative. Familiar examples are protamine insulin and globin insulin; the former being used in the form of a suspension, buffered to *p*H 6·9 to 7·3, the range of minimum solubility. When injected, this form of insulin not only has a more prolonged effect than the corresponding dose of simple insulin, but the hormone is liberated at a more uniform rate. Globin insulin is injected as a clear, acid aqueous solution, the complex being precipitated on coming into contact with the more alkaline tissue fluids. Both these preparations contain traces of zinc chloride which prolongs the action still further.

Another interesting compound or complex of this type has been reported recently by Barnard and Saperstein[10] who found that an insoluble streptomycin "insulinate" was formed when solutions of the two substances were mixed. The separated precipitate injected into rabbits in the form of a suspension, was found to lower the blood sugar, while subcutaneous injection into diabetic patients gave blood sugar curves comparable to those obtained after administration of the protamine or globin conjugates.

A somewhat different approach to the problem was made by Loeve[11] and co-workers who prepared a protein penicillin complex by freeze-drying a sterile solution containing a mixture of penicillin and gelatin. The resulting product in which the crystals of penicillin were enmeshed by the protein, was then rendered insoluble by immersion in an acetone solution of formaldehyde. Prolonged serum penicillin levels were observed both in animals and humans following a single subcutaneous injection of the finely powdered complex suspended in (propylene) glycol containing a small proportion of Tween 80 as dispersing agent.

In addition to proteins there are many other organic compounds and ions which form, with specific drugs, complexes or salts which are relatively insoluble or only slowly available from the "pool." Again penicillin must be mentioned for this antibiotic forms insoluble complexes with some basic dyes, some anæsthetics, and a few of the synthetic antimalarials. All these complexes when injected in adequate doses maintain therapeutic blood levels for several days. Procaine penicillin is the outstanding example of this type of compound and so far is the only one that has come into general clinical use. Its solubility in either oil or water is very low, being equivalent to about 7000 I.U./ml. in either vehicle. For presentation as an aqueous suspension, a suspending agent such as sodium carboxy-methylcellulose is necessary to prevent the solid from settling out in the syringe or blocking the needle. A small amount of a suitable detergent is added to effect good dispersion. Although such an aqueous suspension may not give as prolonged effective blood levels as a suspension in oil and aluminium stearate, its injection is much less painful and the occasional inflammatory reaction following the injection of the oily preparation is avoided. This is especially true if the oil and beeswax injection is the subject of comparison.

*The effect of the solubility of the vehicle in tissue fluids and of its viscosity:* Under this heading it will be convenient to mention the use that has been made of the emulsion form of injection. The administration of an oily suspension was one of the first methods used for prolonging the effect of a drug. Leyton[12], in 1929, claimed to have significantly prolonged the action of insulin by injecting a suspension of the pure dry material in castor oil. Since then many drugs have been injected suspended in various vegetable oils, but the method gives neither an adequately prolonged action nor a sufficiently uniform rate of release.

Attempts have been made to control the release of water-soluble drugs by preparing water-in-oil emulsions. Perhaps the first of this type was suggested by Strauch[13], who used as his continuous phase a mixture of "metacholesterol," myricin and almond oil. The author claimed prolonged effects after the injection of "repository" emulsions containing, as dispersed phase, solutions of adrenaline, iodine, insulin and other drugs. Experiments carried out on mice have demonstrated that, using this form of depot, it is possible to inject many times the normal lethal dose of strychnine without causing death. The animals showed marked response to vibration for some hours after the injection.

Taylor and Court[14] employed the same principle for the preparation of a long acting injection of extract of pituitary, posterior lobe, for use in diabetes insipidus. They reported that two injections weekly of the emulsion were sufficient to ensure complete control of urinary output, with none of the usual undesirable side effects consequent upon injection of large doses of the simple extract. An elaboration of Strauch's repository injection is the subject of a patent[15], a typical " example " in which is

| | |
|---|---|
| Olive Oil ..... | 25 |
| Water ..... | 20 |
| Sodium Oleate ..... | 1·5 |
| Myricin ..... | 1·5 |
| Cholesterol ..... | 1·5 |
| Strophanthin ..... | 0·2 |

suggesting that a mixed emulsion is formed and that the liberation of the drug depends largely upon the stability of the emulsion. It is claimed in this patent that the rate of release of the medicament can be controlled by the use of " regulators "; acceleration being brought about by an inclusion of camphor, or salts of bile acids, of aromatic acids such as benzoic and cinnamic or of alcohols, while retardation is effected by inclusion of cholesterol or of organic or inorganic salts of calcium. It will be realised that extreme care is necessary in the formulation and preparation of injections of this kind, while production on a large scale involves great practical difficulties.

*The effect of the viscosity of the vehicle :* Highly viscous aqueous injections have been used for many years in the preparation of injections for prolonging action. Quite high concentrations of gelatin, for example, have been employed for extending the duration of action of morphine salts. Such injections may be either highly viscous liquids or even gels at normal temperatures, and require the application of heat immediately before use. It was reported at the 1st Congress of Antibiotics[16] held in Milan in 1949 that 10 to 15 per cent. solutions of gelatin had been employed for the administration of penicillin (form not known). Intramuscular injection of 200,000 I.U. resulted in the bacteriostatic concentration of the antibiotic in the blood for periods up to 8 to 10 hours. Administered intravenously, similar results were obtained, while by the intraspinal route, effective blood levels were maintained for periods varying from 24 to 72 hours.

*Pitkin's Menstruum :* G. P. Pitkin has devised a medium based on gelatin, for the purpose of reducing the rate of absorption of water-soluble drugs given either intramuscularly or subcutaneously. It has become known as Pitkin's Menstruum[17] and consists of an aqueous solution of:

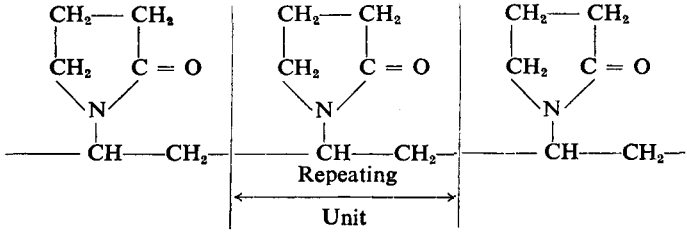
| | |
|---|---|
| Gelatin ..... | 12 to 30 per cent. |
| Dextrose ..... | 5 to 12 per cent. |
| Acetic Acid ..... | 0·3 to 1·5 per cent. |

It is said to be suitable for the administration of preparations of adren-

aline, ephedrine, morphine, etc., where prolonged therapeutic action of these drugs is desired. An interesting application of Pitkin's Menstruum is its use in connection with the injection of heparin[18]. Although heparin is a safe and effective anticoagulant, it is short acting. Apart from its cost, its use is limited by the necessity for its continuous, or frequent intermittent, intravenous administration. By giving a single, deep, subcutaneous injection of the appropriate quantity of heparin, dissolved in the gelatin-dextrose medium, the action of the drug can be made to last for up to 24 hours. Pain at the site of injection was, however, reported, and in some cases, severe local reactions developed. It is evident that some modification of the formula is necessary.

Another means of achieving slow absorption is the use of a suitable mixture of polyvinyl alcohols or their water-soluble derivatives with a solvent for the polyvinyl alcohols[19].

*Polyvinylpyrrolidone:* This is a polymer of variable molecular weight with the following structural formula.




It is very soluble in water, yielding somewhat acidic solutions of high viscosity. Solutions of polyvinylpyrrolidone were used in Germany during the war as a plasma substitute[20], a 3·5 per cent. solution in association with certain electrolytes to the following formula, giving a product with a colloidal osmotic pressure approximating that of whole blood[21]:—

| | | |
|---|---|---|
| Polyvinylpyrrolidone ..... | 35 | g. |
| Sodium Chloride ..... | 8 | g. |
| Potassium Chloride ..... | 0·42 | g. |
| Calcium Chloride ..... | 0·5 | g. |
| Magnesium Chloride ..... | 0·005 | g. |
| Hydrochloric Acid, N ..... | 17 | ml. |
| Sodium Bicarbonate ..... | 1·68 | g. |
| Water to ..... | 1000 | g. |

Thrower and Campbell [22] in an investigation into the possibilities of this solution as a plasma substitute, found that the solution is more stable in the presence of a trace of free carbon dioxide.

Apart from the use of polyvinylpyrrolidone as a plasma substitute, a 25 per cent. solution of this polymer has been used as vehicle for the administration of insulin, the release of which was thereby regularised and and the hypoglycæmic action prolonged. This retarding effect, which increases with concentration of the polymer, has been utilised for the preparation of depot injections of several other drugs. De Seze *et al.*[23]

used a solution containing 2 per cent. of procaine hydrochloride in a 20 per cent. solution of polyvinylpyrrolidone for infiltration anæsthesia. The duration of action of the procaine was definitely increased, being 2 to 3 times that resulting from the use of the simple aqueous solution. The authors remark that none of the side reactions—giddiness and profuse perspiration—were manifested in a patient normally intolerant to the drug.

Quevauvillier[20] and Roux, *et al.*[24] refer to the use of the hypertonic solution (20 per cent.) of polyvinylpyrrolidone as " véhicule-retard " for administration of drugs intramuscularly. They also report retarding action when drugs are administered intravenously in this form; for example, the urinary elimination of quinine was delayed in the rabbit. Intravenous injection of soluble hexabarbitone and of thiopentone in this vehicle also resulted in prolonged action. Such effects produced by intravenous injection were attributed to adsorption of the drugs on the micelles of the colloid.

Lederer[25], as a result of clinical trials in three cases of diabetes insipidus, considered that the use of this technique may be regarded as a valuable improvement in the treatment of this disease with posterior lobe extracts. He reported the effectiveness of much smaller doses of the hormone with marked prolongation of the antidiuretic action; also elimination of the disagreeable symptoms usually produced by the use of a simple posterior pituitary extract. Attempts to prolong the action of adrenocorticotrophic hormone by giving depot injections compounded with polyvinylpyrrolidone, have so far proved unsuccessful.

## Some Notes on Oils and Other Non-Aqueous Solvents Used for Intramuscular Injection.

Although the formulation of an oily injection may appear to need little consideration other than e.g. the choice of an oil having the required solvent action for the drug, it is suggested that the therapeutic effect of the drug may depend to a much greater extent upon the nature of the vehicle than is generally realised. The conflicting reports, pharmacological and clinical, regarding the activity of compounds injected in oily solution may sometimes be due to the use of different solvents by different workers, or the use of the same solvent in different degrees of purity. Budowsky and Markley[26] in a recent review on sesame oil emphasise the fact that this contains several minor constituents such as sesamin and sesamol and suggest that these, which do not occur in other oils, may account for reports of its toxicity[27] to adrenalectomised rats. (The toxic material was found in an alcohol-soluble fraction.) Cruz *et al.*[28] reported the development of purpuric lesions in the skin of dogs into which œstradiol benzoate in sesame oil had been injected. These lesions did not occur when sesame oil alone was used or when other vegetable oils were employed as vehicles—except, to a slight extent, soybean oil. On the other hand, Brown *et al.*[29] concluded that sesame and maize oils were superior to arachis and cotton seed oils as carriers for the preparation of

intramuscular injections on the grounds that they were more quickly absorbed from the tissues, were less antigenic and less irritating.

Although perhaps of little or no clinical importance, the marked difference between the toxicities of solvents to intact and adrenalectomised animals respectively, it is of great significance at that stage of formulation where collaboration between the pharmacologist and the pharmacist is required to decide the ultimate form of presentation of a drug. The increased sensitiveness of adrenalectomised animals to many substances, even those normally regarded as physiologically inert, has been demonstrated by many workers, and as a generalisation it may be asserted that any substance will cause death in these animal preparations in a dose one-fifth to one-twentieth of that lethal to the intact animal[30]. Even a normal body constituent such as urea is found to be much more toxic. As examples, some recently determined values[31] for commonly used solvents are given below:

| Solvent | Ratio of Toxicity. Adrenalectomised (intramuscular) normal mice. |
|---|---|
| Propylene Glycol, B.P.C. ... ... ... | 15 |
| Arachis Oil ... ... ... ... | 6 |
| Glyceryl Mono-oleate, U.S.P. ... ... | 8 |

As Whittet[32] pointed out last year, propylene glycol is a useful addition to an all too short list of solvents available for parenteral use, and even bearing in mind the abnormal toxicity quoted above there is a considerable margin of safety where the human patient is concerned and where injections are likely to be few.

## Effect of Solvent on Rate of Release of Drug.

*Solvent Immiscible with Water.* For a given drug injected in the form of a solution in a solvent immiscible with water such as oil, the rate of diffusion from the depot will be governed by the solvent/water (tissue fluid) partition coefficient. The more this is in favour of the oil, the slower is the passage of the drug from the "pool." The surface area of the depot also affects the rate of release but this factor will be considered later. The profound effect of the distribution ratio of the drug between solvent and water was demonstrated in a recent pharmacological experiment[33] involving the use of adrenalectomised dogs. In this it was found that very large doses of deoxycortone acetate, injected in ethyl oleate, were required to maintain a normal electrolyte balance in the animals. A change of solvent, namely to a mixture of arachis oil and ethyl oleate, soon caused the death of the animals owing to the now rapid transference of the steroid from the depot.

The problem of the choice of suitable solvent is still further complicated when the administration of a mixture of steroids is demanded. An outstanding example is an oily injection of the total steroids of the suprarenal cortex. Here we are confronted with a mixture of closely allied compounds which can be partly fractionated by partition between benzene

and water into the mineralo-corticoids and gluco-corticoids respectively. There is unlikely to be a uniform rate of release of both groups of steroids from any *one* of the commonly used solvents, and this may account for reports in both the pharmacological and clinical literature to the effect that certain oily preparations of total corticoids "appear to consist predominantly of gluco-corticoids."

*Solvent Miscible with Water:* When a water-miscible solvent is used to prepare an injection solution of a water-insoluble drug, as for example the solution of a steroid hormone in propylene glycol, the solvent after injection will be more or less rapidly diluted by the tissue fluids and the drug precipitated. The effect will be much the same as that produced by the injection of an aqueous suspension of the drug, except for that resulting from a possible modification of the size and shape of the particles.

*Surface Area of the Depot:* When an oily preparation is injected it is the surface area of the implanted globule rather than its volume which determines the rate of release of the drug. It follows that a somewhat more rapid effect will result from the administration of a given volume if this is divided and injected into two sites. This obtains, equally, if it is decided to present a drug in the form of pellets.

*Implantation Pellets:* The subcutaneous implantation of compressed or fused tablets or pellets is now a well-established technique of depot therapy and is recognised by the U.S.P.XIV. The method, originating with Deansley and Parkes[33], is applied most successfully to substances of the steroid hormone class since these, apart from being only slightly soluble in tissue fluids, also possess the physical characteristics which are conducive to the production of homogeneous tablets. The amount of drug absorbed from a 125 mg. pellet of deoxycortone acetate is of the order of 0·5 mg. daily, so that a patient who has been maintained on 4 mg./day will theoretically require the implantation of 8 pellets for a steady maintenance supply for a period of about 8 months. Only about 70 to 80 per cent. of the implanted drug is absorbed before the rate of release of the hormone falls below that required for full maintenance. This is usually due solely to the reduction in surface area, but is sometimes due to the formation of more or less impenetrable fibrous barriers around the pellets. Attempts have been made, with varying success, to apply the technique to a variety of substances having a greater solubility in water than the steroids, e.g., adrenaline[34], insulin and protamine insulin, using cholesterol as retarder[35].

## Injections of Penicillin

The formulation of penicillin preparations as a whole has been a challenge to pharmacy ever since this antiobiotic first became available for clinical use. The speedy excretion of penicillin from the body and its rapid destruction by the acidity of the gastric juice and by the coliform organisms of the lower digestive tract, combined with its initial scarcity and cost, soon indicated that some form of repository injection was needed for systemic treatment.

The history of penicillin therapy is so recent and so familiar to all that it does not need to be dealt with here in detail. Almost all the devices of depot therapy so far described have been employed in the formulation of injections of penicillin, and only one special case will be mentioned, namely, the use of aluminium stearate in the oily suspensions of the sodium and procaine salts. Both these forms of penicillin, like other substances prepared as suspensions in oil, tend to settle to a more or less compact mass which is difficult to redisperse uniformly. Incorporation of a small quantity of aluminium stearate to form a gel (a technique developed by Buckwalter and Dickinson[36]) resulted in a product which showed greatly improved dispersion and therapeutic blood levels. Floyd[37] has dealt very fully with the effects on the efficacy of the suspension of (1) varying the type of aluminium stearate used and (2) controlling the particle size of the penicillin salt. The same author has also advanced a theory for the mechanism whereby the aluminium stearate brings about the slow release of the drug.

Floyd's conclusion that the most satisfactory preparation is one containing procaine penicillin of small particle size has since been confirmed by many large-scale clinical trials. Unfortunately it is still not possible to describe in definite chemical or analytical terms the most suitable type of aluminium stearate.

In the above-mentioned paper, the result of the animal test (resistance to infection with *Streptococcus pyogenes*) indicated that the fine particle penicillin salt was most effective with aluminium stearates whose aluminium/stearic acid ratios corresponded to the mono- or tri-salts respectively, and it will be recalled that in the American literature it is always aluminium monostearate that is called for.

From the point of view of the preparation of a stable suspension which also exhibits thixotropy—an important property with respect to easy handling in the syringe—it is possible to use aluminium stearates of a wide range of values for the aluminium/stearic acid ratio, percentage of free stearic acid and other analytical data. In practice, samples producing final products of good dispersion and giving the desired prolongation are those which appear to consist of a mixture of mono- and di-stearate. The criterion, as far as suspension stability of the final products is concerned, is that the aluminium stearate in oil base should possess the property of plasticity. The addition of the relatively high proportion of solid penicillin salt then seems to produce the required degree of thixotropy.

With regard to the mode of liberation of sodium and procaine penicillin from the oil depot, attention is called to the interesting *in vivo* microscopic study carried out by Peck[38]. Small quantities of both sodium and procaine penicillin suspensions were injected into the subcutaneous and intramuscular tissues of anæsthetised mice, and the injected masses were examined over a period by transillumination. As the oil vehicle dispersed through the tissues the smaller crystals of sodium penicillin dissolved and the droplets of solution remained completely surrounded

by oil. Many of the larger crystals became incompletely surrounded by the oil, others formed larger droplets of solution which tended to break through the oil. This transfusion did not take place in the presence of 5 per cent. aluminium stearate, and a double emulsion, penicillin solution/oil/tissue fluids, appeared to form.

With the procaine penicillin, however, due to its low solubility no obvious solution even of the small crystals was noticed—these were seen to persist for many hours and to retract from the edge of the oil mass. Large crystals occasionally broke through the oil. Once again the aluminium stearate preparation appeared to possess greater stability, but in this case there was no visible evidence of emulsion formation nor was it possible to determine if the stearate formed a pellicle around the procaine penicillin. It is interesting to note that the double emulsion did not form when sodium penicillin was suspended in oil with only 2 per cent. of aluminium stearate.

*Clinical Results.* The persistence of effective penicillin levels in the blood of patients after treatment with various types of depot injection has been studied by some American workers[39]. A summary of the results of their investigation, published recently, is given in the following table.

| Type of Preparation | Number of Patients | Duration in Hours of Blood Levels of 0·05 Unit or More per ml. Dose (intramuscular) in Units | | | |
|---|---|---|---|---|---|
| | | 300,000 | 600,000 | 900,000 | 1,200,000 |
| Penicillin in oil and wax ... ... ... | 198 | 18 | 36 | 42 | — |
| Procaine penicillin in oil ... ... ... | 63 | 66 | 56 | 76 | — |
| Procaine penicillin in oil (large particles with 2 per cent. of aluminium monostearate)... | 120 | 51 | 62 | 66 | 70 |
| Procaine penicillin in oil (micro-particles with 2 per cent. of aluminium monostearate)... | 208 | 61 | 88 | 120 | 158 |
| Procaine penicillin in aqueous suspension... | 39 | 42 | 48 | — | — |

From these results it was concluded that the preparations could be placed in the following (descending) order of effectiveness.

1. Procaine penicillin (small particles) with 2 per cent. of aluminium monostearate.
2. Procaine penicillin (large particles) with 2 per cent. of aluminium monostearate; procaine penicillin in oil.
3. Procaine penicillin in aqueous suspension.
4. Penicillin in oil and wax.

## Increasing Rate of Absorption

In contrast to the methods so far considered, and which have been designed to prolong action, the opposite effect may be obtained by the use of hyaluronidase. Although the action of this enzyme is at present

the basis of a clinical technique rather than of formulation, its unique effect is thought to be of sufficient interest to be worthy of mention.

Hyaluronidase is a mucolytic enzyme which, when added to fluids injected into subcutaneous tissues, produces rapid spreading and absorption of the injected material. This effect is brought about by hydrolysis of hyaluronic acid, the polysaccharide present in the interstitial spaces, and lasts for about 24 hours.

Kirby and co-workers[40] reported the use of hyaluronidase with local anæsthetics and found it possible thus to anæsthestise a larger area, although the duration of the anæsthesia was shortened, apparently because of the accelerated absorption.

Moore[41] studied the effect of injecting hyaluronidase with amethocaine in a series of nerve blocks and found that the mixture had a more rapid analgesic effect than amethocaine alone, and that the effect lasted for a shorter period unless vasoconstrictors were used at the same time.

Possibly hyaluronidase shows its greatest clinical value when used for hypodermoclysis in infants. Thus it is reported that the addition of 10 to 20 mg. of this enzyme to 150 ml. of M/6 sodium lactate clysis permitted the administration of this volume in 60 minutes, whereas by the usual technique for drip hypodermoclysis only 75 ml. could be introduced in 4 hours. Actually the fluid began to spread within about 10 minutes after injection, and there was little or no swelling.

Evans *et al.*[42] state that for subcutaneous administration of physiological saline solution, saline-glucose solution, etc., through the anterior abdominal wall, the use of an adequate quantity of hyaluronidase permits of continuous injection of fluid at the rate of 100 to 300 ml. in 5 minutes.

Unfortunately hyaluronidase is not very stable in solution, and it is therefore necessary that it should be freshly dissolved to obtain the best results. A solution of the enzyme may be injected in the skin first, and the fluid then passed through that site, or the enzyme may be simply dissolved in the infusion solution. Alternatively, an injection of hyaluronidase may follow a preliminary injection of a few ml. of the main solution.

### Contact Lens Solutions. A Problem for Further Research

The greatly increased use of contact lenses would appear to justify some comment with regard to the solutions used in connection with the wearing of these optical devices. The purpose of the contact lens is to correct the effects of abnormal curvature of the cornea. The lens is of plastic and is designed to rest on the scleral area of the eyeball and to extend over the corneal surface without making actual contact with the cornea itself. This leaves a space between the anterior surface of the eyeball and the contact lens, to fill which solutions of various substances such as gelatin, glucose and normal saline have been used. Most subjects complain of a fogging or clouding of vision within a few hours after insertion of the lens. This is due to swelling of the epithelial layer of the cornea, caused perhaps by interference with the elimination of carbon

dioxide and other products of metabolism. Hind and Goyan[43] record the results of a large-scale experiment in which patients were asked to select a solution which gave maximum wearing time. The most popular preparations were found to be (a) a borate buffer containing small concentrations of sodium, potassium and calcium chlorides, and (b) solutions containing 1·5 and 2 per cent. respectively of sodium bicarbonate. None of these solutions, however, ensured a sufficiently long period free from fogging. This appears to be a problem calling for collaboration between the physiologist, the pharmacist and, possibly, the expert in plastics.

## Flavouring

At one time the observation that the most active medicinal substances had a bitter or disagreeable taste tended to endow all such substances with remedial properties. The psychological effect of taking bitter or obnoxious preparations may still have some influence, but modern practice tends towards presenting bitter drugs in the most palatable form possible. When tablets or capsules are practicable, this is the chosen form of presentation, but for infants or young children a liquid preparation is often essential and many efforts are being made to find suitable and effective masking agents. Even with adults it is now recognised that an oral preparation which creates nausea or other unpleasant sensation, especially on repeated dosage, may defeat its purpose, and this is quite particularly true where children are concerned.

On the other hand, the formulation of potent drugs to give preparations of the elixir type has been subjected to considerable criticism, because of the attraction such products have for children. Such criticism, however, might equally be applied to sugar-coated tablets! To prevent overdosage in adults it has been proposed[44] to cover tablets of barbiturates with a coating containing sub-emetic doses of emetine, etc. This ingenious suggestion might well be applied to tablets of other potent drugs so as to avoid accidental overdosage in children.

Little is known as to the mechanisms of taste and smell. El-Baradi and Bourne[45] tentatively suggest that the primary mechanism of both these senses may be that of interference with one or more enzymes by the substance possessing odour or taste. Bourne[46] has shown that alkaline phosphatase is present in relatively high concentration in the epithelium overlying the taste buds and also in the olfactory mucosa. Vanillin was found to inhibit strongly the gustatory phosphatase; a small gustatory inhibition was noted with infusions of tea and capsicum, but sugar, sodium chloride and quinine had no effect. Infusions of coffee, oil of aniseed and oil of peppermint had a slight inhibitory effect. El-Baradi and Bourne state that they are pursuing this line of investigation, finding it difficult to make any deduction from their results so far.

Lankford and Becker[47] have carefully studied the problem of flavouring with respect to masking the taste of ammonium chloride and quinine, using various natural and synthetic fruit-flavoured syrups. They found that flavours which would cover the initial salty taste of ammonium

chloride would not always mask the obnoxious, persistent taste of this drug. The addition of acid to imitation fruit flavours increases their covering power, probably due, according to the authors, to the tartness temporarily inhibiting the action of the taste buds. Raspberry syrup of the U.S. National Formulary, acidified imitation raspberry, wild cherry and grape syrups, syrup of cocoa, U.S.P., cherry syrup N.F., and glycyrrhiza syrup, U.S.P., were found best for masking the initial salty taste of ammonium chloride, while vanillin-flavoured and maple syrups were among those most effectively masking its persistent after-taste. For disguising the bitter taste of quinine hydrochloride, the authors found syrup of cocoa to be the most effective. They observe that quinine hydrochloride when present in higher doses becomes even more obnoxious in the presence of some of the flavourings used.

Experience has shown that the problem of flavouring or masking distasteful drugs may be approached in one or more of the following ways: (1) To use as flavouring agent a pleasantly flavoured substance which has also something in common, in its flavour, with the bitter drug. The use of orange with gentian and quinine is an example of this method of approach. (2) To use substances such as menthol or oil of peppermint to produce a mild local anæsthesia. (3) To use as menstruum colloidal solutions such as mucilage of acacia. The mechanism involved here is not known, but such solutions are certainly effective in many cases. (4) To use moderate concentrations of sodium chloride, in which the bitterness of some drugs is lessened.

Obnoxious flavours of oil-soluble substances can, of course, be dealt with by producing emulsions of the oil-in-water type, but it is less often possible to utilise this effect of emulsification for water-soluble substances, which of course should form the disperse phase.

## New Aids to Formulation

Under this heading will be given a few notes on compounds possessing special properties which make them of particular value in the formulation of substances otherwise difficult to handle or to present in the most effective form.

*Polyethylene Glycols:* These condensation polymers of ethylene oxide and water are represented by the general formula $HOCH_2.(CH_2OCH_2)_n CH_2OH$ (where n varies from 7 to 85 or more). They are characterised by their chemical inertness and complete solubility in water. They vary in consistency according to molecular weight, polyethylene glycol 400 occurring as a viscous liquid, while polyethylene glycol 4,000 resembles paraffin, both in appearance and texture. Both these compounds are included in the U.S.P.XIV for use as ointment bases, having been shown to be free from toxicity and to give rise to no reactions when used for this purpose. By blending these compounds in suitable proportions, it is easy to control the consistency of an ointment base, and they readily lend themselves to extemporaneous use. The polyethylene glycol oint-

ment of the U.S.P. consists of equal parts of the two official polyethylene glycols.

The oral toxicity, both acute and chronic, of these glycols appears to be of a very low order and preliminary work which has been carried out to determine the extent of their gastro-intestinal absorption in rats and human beings shows that excretion is almost complete. The physical properties of these glycols made their use very attractive as a vehicle for the topical application of pencillin, because of the slow or incomplete release of this antibiotic from entirely fatty bases and because of its instability in other hydrophilic bases. Unfortunately, although penicillin incorporated in such bases is readily released, it is, in these media, somewhat rapidly destroyed. The loss of activity may be due in part to the slight hygroscopicity of these polymers (especially of those of lower molecular weight), but appears to be caused mainly by their acidity. These bases have been used as vehicles for the presentation of substances difficult to formulate, such as salicylanilide, cuprammonium hydroxide and chloramphenicol.

*Polyethylene Glycols as Suppository Bases:* Charounat *et al.*[48] examined the relative usefulness of cocoa butter, glyco-gelatin and polyethylene glycol (4000?) as bases for the preparation of suppositories. They employed guinea-pigs as test animals and recorded, by means of thermocouples, the temperatures of the ears of the animals after administration of suppositories each containing 5·5 mg. of the methyl ester of nicotinic acid. The authors published the temperature curves, and from these it is obvious that, from the point of view of duration of action, maximum intensity and overall effect, the bases could be placed (in order of decreasing efficiency): glyco-gelatin, cocoa butter, polyethylene glycol. Perhaps their most important observation was the frequency with which suppositories made with the last-mentioned base were rejected, both by the test animals and by human beings.

*Polysorbate 80:* This is a polyoxyethylene derivative of sorbitan monooleate, and is representative of a comparatively new group of non-ionic surface-active agents. It is also included in the U.S.P. XIV but is used officially only for the preparation of benzyl benzoate chlorophenothane lotion. Apart from its use as an emulsifying agent a unique application depends upon its solubilising power for concentrates of vitamin A[49] and other oil-soluble vitamins making it possible to obtain these otherwise water-insoluble vitamins in high concentration in an aqueous medium, from which the vitamins are then rapidly and completely absorbed. Polysorbate 80 has also been administered, as such, for the purpose of increasing fat absorption from the intestinal tract in patients suffering from steatorrhœa[50] and other such gastro-intestinal disorders.

*Microcrystalline Waxes:* Microcrystalline waxes, sometimes termed "amorphous paraffin wax," are obtained by distillation of the residue from certain crude oils and have relatively high molecular weights. They consist mainly of saturated hydrocarbons, other than straight chain paraffins. Microcrystalline wax is distinguished from paraffin wax by its

small crystalline structure, its toughness and its flexibility. It has been used to prepare ointment bases[51] containing high proportions of liquid paraffin, the final products being smooth and homogeneous, and resembling soft paraffin in texture. These bases are mentioned here, because of their unusual properties, dependent upon their relatively small thermal coefficient of viscosity. They maintain a suitable consistency over a wide temperature range and do not liquefy unduly at temperatures occurring in tropical climates. Even at such elevated temperatures as these, they retain adequate suspending power for incorporated solids. Comparative ageing tests have shown these bases to have a certain superiority over other ointment bases; while *in vitro* tests have demonstrated a more rapid release of incorporated medicaments than from soft paraffin.

## REFERENCES


1. Gaddum, *Brit. med. Bull.*, 1946, **7**, 280.
2. Todd, *J. Pharm. Pharmacol.*, 1950, **2**, 919.
3. Anon., *The Glaxo Volume*, No. 3.
4. Trumper and Hutter, *Science*, 1944, **100**, 432.
5. Reid, *Proc. Soc. exp. Biol.*, 1947, **66**, 650.
6. *Bull. Johns Hopkins Hosp.*, 1951, **88**, 276.
7. Young, *Chem. Soc., Ann Rep.*, 1945, **42**, 214.
8. Edkins, *Pharm. J.*, 1950, **164**, 155.
9. Sakamoto, Gordon and Eisenburg, *Proc. Soc. exp. Biol.*, 1951, **76**, 406.
10. Barnard and Saperstein, *J. Amer. pharm. Ass.*, 1951, **40**, 55.
11. Loeve, Sobel and Allure-Weber, *J. Lab. clin. Med.*, 1949, **34**, 1.
12. Leyton, *Lancet*, 1929, **216**, 756.
13. Strauch, *J. Amer. med. Ass.*, 1929, **92**, 1177.
14. Taylor and Court, *Pharm. J.*, 1939, **43**, 239.
15. *Brit. Pat.* 417,715.
16. Anon., *J. Amer. med. Ass.*, 1949, **139**, 869.
17. *U. S. Pat.* 2,530,480.
18. Goodwin and Macgregor, *Lancet*, 1950, **259**, 667.
    Muir, *Lancet*, 1950, **259**, 671.
19. *G. Pat.* 701,779.
20. Quevauviller, *Anesthésie Analgésie*, 1949, **6**, 296.
21. Bordreaux, *Paris, Méd.*, 1945, No. 3, 23.
22. Thrower and Campbell, *Lancet*, 1951, **260**, 1096.
23. De Sèze, Ordonneu and Denil, *Rev. du Rhumatisme*, 1947, **14**, 138.
24. Roux, Jacquot and Huguenard, *Anesthésie, Analgésie*, 1949, **6**, 331.
25. Lederer, *Acta endocrinol.*, 1949, **2**, 307.
26. Budowski and Markley, *Chem. Rev.*, 1951, **48**, 125.
27. Bruce and Tobin, *Endocrinology*, 1940, **27**, 956.
28. Cruz *et al.*, *Rev. brasil Biol.*, 1945, **5**, 367.
29. Brown, Wilder and Schwartz, *J. Lab. clin. Med.*, 1944, **29**, 259.
30. Pincus and Thimann, *The Hormones*, Vol. ii (1950).
31. Lockett, *Private communication.*
32. Whittet, *J. Pharm. Pharmacol.*, 1950, **2**, 934.
33. Deansley and Parkes, *Proc. roy. Soc., B.*, 1937, **124**, 279.
34. Parkes, *J. Endocrin.*, 1942-44, **3**, 220.
35. Vargas, *Lancet*, 1949, **256**, 598.
36. Buckwalter and Dickison, *J. Amer. Pharm. Ass.*, 1948, **37**, 472.
37. Floyd, *J. Pharm. Pharmacol.*, 1949, **1**, 747.
38. Peck, *Fed. Proc.*, 1950, **9**, 306.
39. Cannon, Slatkin, Chester and Moses, *J. Amer. med. Ass.*, 1951, **145**, 1031.
40. Kirby *et al.*, *Surgery*, 1949, **25**, 101.
41. Moore, *Anæsthesiology*, 1950, **11**, 470.
42. Evans, Perkins and Garsford, *Lancet*, 1951, **260**, 1253.
43. Hind and Goyan, *J. Amer. pharm. Ass. (Pract. Pharm. Ed.)*, 1950, **11**, 732.

44. Riccio, *Riforma Med.*, 1950, **64**, 1164.
45. El-Baradi and Bourne, *Science*, 1951, **113**, 660.
46. Bourne, *Nature*, 1948, **161**, 445.
47. Lankford and Becker, *J. Amer. pharm. Ass.*, 1951, **40**, 77.
48. Charounat, *et al.*, *Ann. pharm. franc.*, 1949, **7**, 627.
49. *Brit. Pat.* 588,298.
50. Jones, Culver, Drummey, Ryan, *Ann. intern. Med.*, 1948, **29**, 1.
51. Foster, Wurster, Higuchi and Busse, *J. Amer. pharm. Ass.*, 1951, **40**, 123.

MR. W. NIXON said:—The advantages of the newer aids to formulation are usually well known, but it is only after extended practical use that their limitations are revealed.

Mention has been made of the fact that the polyethylene glycols are completely soluble in water. This limits the amount of aqueous liquid that can be incorporated into an ointment prepared with these compounds. The reported limit is 3 per cent., and if an amount in excess of this is to be introduced, a stabiliser is required. The addition of 5 per cent. of cetyl alcohol is said to allow the introduction of 20 per cent. of aqueous liquid. Ointments containing polyethylene glycol and propylene glycol have been used, such as polyethylene glycol 4000, 45 parts, and propylene glycol, 55 parts. An ointment of bacitracin prepared with this base lost 50 per cent. of its potency in a week when stored at room temperature. The ointment, in some cases, caused a burning sensation. An ointment containing bacitracin, prepared from a mixture of polyethylene glycols, no propylene glycol being added, only retained its activity if stored in a refrigerator; an ointment base of the anionic type was needed to preserve the activity at room temperature.

The list of suspending agents has been increased by the addition of the cellulose derivatives, bentonite magma, the polyethylene glycols of lower molecular weight, etc. Cellulosic substances such as sodium carboxymethylcellulose have some incompatibilities. A new soluble cellulose, sodium cellulose sulphate, giving medium and low viscosity solutions, is reported to be compatible with a large number of inorganic salts. Medicated jellies containing cellulose derivatives and 10 per cent. of glycerin have been used for the treatment of skin conditions, but have been found to dry out, leaving behind a platelike material which tends to crack and sets up irritation at the edges of wounds. Since it was found that more than 10 per cent. of glycerin altered the conditions of drainage from the wound, the use of the cellulose derivatives has been discontinued in at least one hospital.

In the U.S.P. XIII bentonite magma was specified as the suspending agent for calamine lotion, but in the present U.S.P. it has been superseded by a mixture of polyethylene glycol 400 and polyethylene glycol 400 mono-stearate. The result of the change of suspending agent is that the finished lotion does not settle on standing. The viscosity of the lotion has been increased by the change, and one wonders if this is really desirable.

The polyoxyethylene derivative of sorbitan mono-oleate has been used on account of its ability to solubilise oils. I have used the monolaurate

in the production of a concentrated peppermint water of B.P. strength for laboratory work, and found that a perfectly clear solution was obtained at first. Dilutions of it were also quite clear. On standing, however, the concentrated solution tended to become cloudy, and this cloudiness seemed to increase and decrease as the temperature of the room fluctuated. On prolonged standing over a period of months a deposit occurred. Is this cloudiness and deposition on standing common? At 37°C. the solution clears.

W. C. Ward in a paper on " Hydrophilic Suppository Bases " has used Tween 61, a polyoxyethylene derivative of sorbitan mono-stearate, as the base. He claims that greater retention is obtained with this base. Other advantages are that it sets to a firm wax at ordinary temperatures, it is not rancid and most medicaments are compatible with it.

It has been stated that coal tar should not be incorporated into hydrophilic ointment bases because these allow of the penetration of the carcinogenic substances present in the tar. Is this an acknowledged fact and is it widely known?

Mr. Nixon concluded with a reference to the value, in good formulation, of all the various subjects included in the pharmaceutical student's curriculum, some of which were thought by the student to have little bearing on the practice of pharmacy.

MR. W. SWALLOW said:—The hospital pharmacist, in one respect, is more advantageously placed than either the manufacturer or the retail pharmacist, because he is able to keep close touch with experimental preparations. For the first assessment of the usefulness of a medicament in a particular vehicle it is not necessary to consider the implications of long storage and exposure to wide ranges of temperature and atmospheric conditions. All that is needed in the first place is to produce a preparation which is stable for a week or so. Of course, if preliminary results are successful it is then essential to review the composition of the preparation with due regard for concentration, stability, preservation and so on, and this is undoubtedly where the hardest work comes in. The fact of being able to make a " trial run " in this way means that time and effort need not be wasted in completely unsuccessful directions.

I think it is a good investment for the hospital pharmacist to experiment with as wide a range as possible of the modern emulsifying, dispersing, wetting and stabilising agents. At the same time, the older substances such as tragacanth, acacia, sugar, alcohol, glycerin, etc., should not be overlooked, because in some directions they can still not be surpassed.

I should like to mention a few applications of some useful aids to formulation. A 25 per cent. streptomycin cream can be made by using a base of wool alcohols, soft and liquid paraffins and sorbitan sesquioleate. This gives a water-in-oil emulsion which favours a slow release of streptomycin and so minimises the risk of local irritation. The preparation has been in successful use for over two years in the treatment

of tuberculous sinuses and other similar areas of infection somewhat cut off from the general circulation.

The polyoxyethylene derivative of sorbitan monolaurate is an effective solubiliser of essential oils and can be used, for instance, to make a clear solution of a pine oil suitable for dilution as a deodorant spray.

It is well known that an activated colloidal aluminium hydroxide is a useful dispersing agent for insoluble powders, and will also produce stable oil-in-water emulsions of low viscosity. This latter fact has prompted its successful use instead of acacia in the glucose-vegetable oil mixture which crops up from time to time as a duodenal drip in uræmia. The preparation is thin enough to go easily through a Ryle's tube. Another use for colloidal aluminium hydroxide is in wetting water-repelling substances such as calcium mandelate. An alternative is to employ sorbitan monolaurate and its polyoxyethylene derivatives: a mixture of equal parts of these two products, in a strength of 0·125 per cent., took 65 sec. to wet 5 g. of calcium mandelate, while under similar conditions the aluminium hydroxide in 5 per cent. concentration took 80 sec., but this result has not been followed by any clinical trial.

In spite of Mr. Eastland's point about overdosage of pleasant-tasting children's mixtures, my own opinion is that the achievement of palatability is valuable enough to outweigh the objections. To this end Mr. Eastland has made some useful suggestions. My own limited experiments lead me to favour plenty of syrup, bright colours (e.g., red or green) and fairly high concentrations of fruit flavours. For example, a favourite premedication for children having tonsil operations is an oral dose of atropine sulphate, and by presenting it in a blackcurrant-flavoured syrup it is taken readily. It is interesting to note that the same syrup without atropine or other medicament is sufficient to pacify infants during dressings or even minor operations.

The rather outmoded effervescent preparation is sometimes worth considering. For instance, the present-day large doses of ascorbic acid can be made pleasant to both children and adults by combining the dry substance with sodium bicarbonate, tartaric acid, sugar and lemon flavour so that an appropriate amount can be stirred in water and taken while effervescing.

MR. DONALD W. HUDSON said:—The production of materials for parenteral medication is ostensibly the field of the manufacturing pharmacist, and the dispensing pharmacist can make little contribution. Pharmaceutical formulation is, however, a subject of such wide application that within it will be found a number of problems which the pharmacist engaged in the dispensing of medicines must be called upon to resolve or to explain almost daily.

In the early part of last century Duncan, of Edinburgh, proclaimed certain basic principles of formulation which would appear to me to be just as applicable to-day, and which can be applied with perhaps equal exactitude to all classes of pharmaceutical formulæ.

The principles called for the careful consideration of the structure of the formula in the following order:—(1) The Exhibit, or principal active

drug. (2) The Synergist, or other drug or drugs which will co-operate in making the principal drug effective. (3) The Adjuvant, or other drug or drugs which will assist or otherwise influence the action of the foregoing two, or will render the preparation more acceptable to the patient. (4) The Corrective, or any further additions necessary to control side reactions. (5) The Vehicle, or medium in which all should be presented.

Formulary prescribing has to some extent eliminated the necessity for the medical practitioner to possess a comprehensive knowledge of the science of formulation and, indeed, the ever-increasing demands of the medical curriculum must relegate this duty to an increasing extent to the pharmacist, who, as each new drug is made available to medicine, must be prepared to give technical advice as to the best method of formulation of the individual prescription. Frequently it is only at a much later date that the manufacturing pharmacist or those engaged in the compilation of the various official formularies presents the drug or combination of drugs with this problem already solved.

A typical example of this position appeared on the introduction of para-aminosalicylic acid, which as recently as 3 years ago required to be extemporaneously formulated and prepared into a solution of the sodium salt by the dispenser by reaction in molecular proportion with caustic soda and subsequent adjustment to a critical *p*H value of 7·4. Rendering the solution palatable for oral, or sterile for intrapleural, use presented other problems to the formulator and dispenser. To-day the sodium salt is readily available in a number of palatable or presentable forms. Formulation has proceeded from the dispensing to the manufacturing stage, but by no means are all the problems solved, as those who have been called upon to prepare tablets or cachets will readily appreciate.

Undecylenic acid is a similar example. The earlier creams and ointments employing this substance frequently required to be formulated in the dispensary. Prescriptions called for an ointment of 5 to 10 per cent. of the acid, or 10 to 20 per cent. of the zinc salt. The technical acid varies considerably in colour and viscosity. The zinc salt occasionally required to be extemporaneously prepared. Here was a typical example in which the vehicle in which the active drug should be incorporated should be given careful study. Was there an optimum *p*H value? Would a paraffin base, a stearic acid base or an emulsifying wax base yield the best results, and in considering the adjuvant how best would the generally unpleasant odour be satisfactorily masked? A number of formulæ have since been published which by their variation indicate that there is still no authoritative answer to these early problems.

With the production of moulded plastic lenses of more precise conformity and greater optical accuracy, solutions for use with contact lenses are becoming a much more frequent dispensing operation. In the past few years considerable research has been undertaken with these solutions, the problems of which are by no means simple. The tinting of these lenses by at least one maker has necessitated further work with all the

accepted formulæ to verify that the solutions do not produce any colour change in the lens or that the introduction of the ultramarine dye into the plastic material has not rendered the lens surface porous to the solutions. I cannot agree with the previous speaker that the principal problem is one of clouding and opalescence. This is only one of many. The major problem is tolerance, and since it is only the solution which comes into contact with the cornea and to a varying extent with the sclera, the solution must be suspect. Tonicity and *p*H value undoubtedly play a most important part, but results in individual cases show great variation. The earlier assumption that a solution corresponding to the tonicity of human tears would be the correct one is in practice far from fact. A tonicity equivalent to 1·4 per cent. sodium chloride solution is but poorly tolerated in the average case, whilst the addition of 0·25 per cent. of sodium bicarbonate to adjust the *p*H value does not appreciably increase the toleration.

Formulations of buffered isotonic solutions (Feldman's using borax, boric acid and sodium chloride with a *p*H range from 7·0 to 8·8) have been used with some considerable success, as have similar solutions formulated by Gifford and Smith using boric acid, potassium chloride and sodium carbonate through a similar range of *p*H values, but perhaps a simple isotonic solution of sodium bicarbonate is as satisfactory as any to many users. It is quite common to issue several different solutions for personal experimentation to fresh cases. Formulation is not infrequently left to the pharmacist, the range of *p*H values only being stated by the prescriber.

Formulation in this field should in my opinion go further than the production of the solution. The user has his or her own particular problem. Small quantities of the necessary solution must be carried about for change. What sort of quantity, and how should it be carried? What is the ideal quantity of solution to issue at a time, bearing in mind that some produce a deposit on prolonged keeping? What should be the requirement of filtration and/or sterilisation? Is it practical to prepare accurately weighed powders or tablets of the solids for the user to make solutions as required? Can any bacteriostatic be included in the formula without producing further intolerance; both *p*-chloro-meta-cresol and all esters of *p*-hydroxybenzoic acid and their sodium salts appear to intensify it. Addition of certain of the antihistamines alone and in combination with a vasoconstricting agent has also been tried in complicated cases.

I should like to add a few remarks to what has already been said about flavouring. The first paper has already referred to the absence of any specific knowledge of the mechanism of taste and smell, and has drawn attention to the investigations which are proceeding in this field of work. It would appear that the time-honoured method of trial and error still remains supreme in determining the efficacy of the various masking agents available. It is encouraging, however, to find that, in an age when each formulated ingredient is required to be specific, serious attention is being given to these aspects of pharmaceutical elegance amongst which should also be included colour. In the past far too little

attention has been paid to these adjuvants in official formulation, with the result that in many cases independent pharmaceutical manufacturers have been able to present a much more attractive product.

Of the 54 mixtures intended for adult use included in the Formulary Section of the British Pharmaceutical Codex 1949 only in 4 cases was no flavouring or sweetening agent considered to be necessary. This alone should underline the importance of this aspect of formulation. In 26 cases, or approximately 50 per cent., chloroform water alone was regarded as adequate. In 10 more liquorice was the flavouring of choice, 8 have the addition of peppermint, whilst the remaining 3 employ cinnamon or aniseed. In the 24 mixtures intended for children the selection is little more inspiring. The only additions to those previously mentioned are caraway, spirit of orange and syrup of wild cherry, none of which can, I think, be regarded as particularly palatable, particularly to a child. The National Formulary offers an even more restricted range of flavouring agents, and the sections devoted to linctuses in both volumes is no more encouraging. Whilst the palatability of medicines intended for adult use is perhaps not so important, a range of simple fruit-flavoured syrups for use in children's preparations could be simply and advantageously formulated. Indeed, such a range is already available to commercial users, adequately coloured and of either acid or neutral reaction. A syrup or suspension of cocoa would also find a useful place, but in a much more restricted field.

The choice of colouring agents appears to be equally restricted. Out of some 50 or 60 available to commerce pharmacy employs about half a dozen. Of the 4 dye solutions included in the formulary section of the B.P.C. only 3 can be regarded as suitable for the purpose indicated. The two Bordeaux dyes are almost identical in colour in neutral solution, leaving the formulator the choice of either yellow or red. Solution of Bordeaux B. cannot be regarded as entirely satisfactory. In alkaline solution it is a poor orange, and in acid solution and particularly in the presence of mineral salts it can precipitate. Amaranth or Bordeaux S. gives much less variation between acid and alkaline reactions and does not precipitate with the salts commonly met with in dispensing. It is the colouring agents of choice in this colour range. Tartrazine solution in the range of yellows is free of any of these faults and it is difficult to understand why it is not more commonly employed.

In recent years a number of fundamental points in simple formulation appear to have been forgotten or overlooked, if not in official formulation certainly in many individually written prescriptions. I refer to such expedients as adjustment of reaction, solubility, viscosity or suspension to assist palatability as opposed to the direct addition of an adjuvant for this purpose. Slightly acid mixtures are usually more palatable than neutral or alkaline ones. The intense bitterness of many drugs can be reduced by administration with, or treatment by, an alkali. Where gels or colloidal suspensions can be produced these will usually be found to be tasteless or nearly so. There is an optimum viscosity of all unpleasant preparations: this should be sought and employed. Where an essential

oil is employed as a masking agent the quantity should be considered in relation to the dose and not the volume. Half to 1 minim per dose is a preferable expression of quantity to a percentage in which the dose volume will vary. I endorse Mr. Eastland's remark that the formulation of potent drugs into highly attractive elixirs has been subject to criticism. This practice is fraught with danger to young and old alike. The duty of the formulator should be to produce a preparation which can be taken without nausea or revulsion but will not invite risk by reason of its elegance.

After nearly 50 years' experience in the preparation of compressed tablets it might be thought that the manufacturing pharmacist had solved all the problems connected with this specialised branch of pharmaceutical formulation, particularly in view of the enormous increase in the popularity of this type of medication. However, this is by no means the case. With the ordinary admixture of drugs little or no difficulty exists. Any combination which the pharmacologist requires can be formulated and produced by the pharmacist, but in some cases the different methods of use to which the tablet will be put has presented fresh problems. In others, it is the nature of the new drug itself which the formulator must combat.

The controversy concerning colouring of both coated and uncoated tablets still continues, but of one thing I am certain, that in so far as the commercial formulator is concerned, coloured tablets have come to stay. From the manufacturers' point of view they offer no technical difficulties, and in some cases considerable advantages. From the dispenser's point of view the same position could be established, and from the public standpoint of any risk involved by reason of their attractive appearance, if this was to be seriously raised it should have been done 25 years ago when chocolate-coated or synthetic chocolate-coated tablets first put in an appearance. It is a little late to raise the issue now.

Formulation of some of the more recent drugs such as para-aminosalicylic acid into white tablets still presents problems possibly due to the presence of moisture or an unduly high humidity at the time of preparation.

There still appears to be no authoritative statement upon the desirable formulation of tablets for sublingual use, particularly in respect of the disintegration rate. The optimum absorption rate can only be obtained by careful formulation of the base or vehicle and by proper selection of a suitable compression load.

The introduction of compressed lozenges into the official formularies suggests further consideration of the obvious advantages of this method of presentation of drugs intended for local oral use. The advantages are many: (1) Accuracy of dose. (2) More accurate control of the duration of application. (3) Prolonged keeping qualities under almost all climatic conditions. (4) Ease and low cost of production. (5) Pharmaceutical elegance. Formulation of the base requires to be accurately balanced against the solubility and absorption rate of

the drug, some requiring much more demulcent principle than others. In each case specific instructions on the nature of the granulation process is called for. In many cases this type of lozenge could well supersede the older variety.

From the application of the new aids to formulation mentioned in the opening paper I should like to select one or two for special consideration from the dispenser's viewpoint and to comment in somewhat general terms upon a number of the others. It is unfortunate that we have so little choice of vehicles for medication by suppositories. That oil of theobroma possesses all the most desirable qualities I do not dispute. Of melting point 33° to 34°C., a readily assimilated food-product, self-lubricating with almost permanent keeping qualities, it is ideal, but it is an oil. Glyco-gelatine also possesses most of the desirable characteristics, but if research could produce a substance which would increase or stimulate the absorption by the mucosa of such substances as chloramphenicol the problem of administering such orally objectionable substances to children would be gone forever.

Of emulsifying agents and microcrystalline waxes I would point out that quite an interesting story could be developed out of the growth of the cosmetic industry utilising many of them. From the potassium, sodium and ammonium stearates which formed the basis of the earlier vanishing creams, has arisen the application of triethanolamine stearate and oleate which are not only of service in preparing cream bases of this nature but have also given to many emulsions a permanency hitherto unobtainable. Glyceryl monostearate was extensively used in the industry before 1939 but it was not until 10 years later that it became official in the B.P.C. Diglycol stearate is yet another agent in very general use. Wool alcohols was in industrial use for many years before its pharmaceutical value was recognised in official formulation. More recent types are the alginates and cellulose products, although it should be noted that methyl cellulose was used in Germany as long ago as 1932. It is interesting to note that aluminium stearate which established itself as a thickening agent in industry some 20 years ago has now been introduced to pharmacy as an adjuvant to certain injections of penicillin. Isopropyl myristate is worthy of the attention of the pharmaceutical formulator. It possesses many valuable assets, it is a barrier which retains its unctuous state through a very wide range of temperatures; it is colourless and odourless and has no tendency to oxidise; it is insoluble in water but readily miscible with paraffin and vegetable oils. Such a vehicle should be of service to the dermatologist.

The CHAIRMAN said he would be interested to know what was the impact of formularies such as the British Pharmaceutical Codex and the National Formulary on retail practice. Problems such as incompatibility, storage, containers and so on were solved for the retail practitioner by those Formularies; but the retailer would be foolish if he thought that no further problems would arise as, for example, had occurred with the introduction of penicillin when he was called upon

without warning to produce sterile preparations. He therefore urged the pharmacist not to rely upon his craft being detailed for him. In preparing monographs for the B.P. and B.P.C., difficulties arose in connection with specifications for purity and characteristics to ensure non-variability of pharmaceutical preparations. It was important that official recognition of new substances should not create bottlenecks. The papers had reflected the changing face of therapeutics and called attention to the new technique such as depot therapy and sublingual medication. With reference to the latter there was now a demand for highly compressed tablets of methyltestosterone. The B.P. had rejected the sublingual route for medication with methyltestosterone as there was insufficient evidence that the drug could be administered advantageously by that route. The pharmacist to-day required a broad background including a knowledge of pharmacology, microbiology and physical chemistry.

MR. A. R. G. CHAMINGS (Horsham) mentioned that the size of deoxycortone tablets for implantation therapy preferred by American endocrinologists was 125 mg. in contrast to the 100 mg. used in this country. Moreover, the Americans used 800 mg. as an initial dose, whereas English endocrinologists were convinced that the maximum dose given initially should not exceed 300 mg. He asked whether Mr. Eastland had any reason for not including ethyl oleate in the list of solvents for parenteral injection, and whether there were any factors such as toxicity to be borne in mind, particularly as the substance was included in the B.P.

MR. J. W. HADGRAFT (London) said that in his experience it was not necessary to limit the amount of aqueous liquid with polyethylene glycols to a concentration of 3 per cent. In developing a series of preparations for the treatment of ringworm of the scalp, he had found that ammoniacal copper oxide was difficult to incorporate in the usual ointment bases whether of an emulsified or non-emulsified type. The water-solubility and waxlike consistence of the polyethylene glycols seemed suitable for the purpose, and a satisfactory ointment was obtained by incorporating 10 per cent. of ammoniacal copper oxide with polythylene glycol 1500. The polyethylene glycol also proved of value in the formulation of pessaries for the treatment of *Trichomonas vaginalis* infection. The difficulty of incorporating phenylmercuric dinapthylmethane disulphonate in oil of theobroma was overcome by the use of a mixture of polyethylene glycols 1500 and 4000. There was little evidence of irritant effect, although in some patients there was evidence of incomplete solution of the pessary. The increasing use of polysorbate 80 underlined the need for an official preparation of the non-ionic type of surface-active compound. It should be possible to formulate a non-ionic variant of the official emulsifying wax which would be valuable for use with organic substances containing cationic radicals and electro-positive nitrogen which were incompatible with the sodium laurylsulphate. An example of the formulation of a substance in short supply was the preparation of an ointment containing cortisone. The problem was solved by the

use of an established ointment base, 40 per cent. of the injection being incorporated in ointment of wool alcohols.

MR. A. W. BULL (Nottingham) said that he believed that the use of polysorbate 80 as described by Mr. Eastland for the preparation of water-soluble products of vitamins A and D was protected by patent rights. He confirmed Mr. Nixon's observation that preparations containing polyoxyethylene derivative of sorbitan monolaurate for the solubilisation of peppermint oil tended to become cloudy. He suggested that it might be worth investigating whether there was any hydrolysis of the solubiliser to lauric acid. The U.S.P. recognised sublingual tablets and stipulated a maximum disintegration time of 4 hours, as against 15 minutes in the B.P. The dose of methyltestosterone being half the oral dose. In view of the general impression in this country that the sublingual route had advantages, it was gratifying to have the Chairman's clarifying remarks. The lack of tolerance of contact lens solutions described by Mr. Hudson as isotonic at 1·4 per cent. might be explained by the fact that the generally accepted concentration for isotonicity was 0·9 per cent.

MR. T. D. WHITTETT (London) pointed out that clinical efficiency was the first criterion, although it might not always be compatible either with consideration for the patient or pharmaceutical elegance. Local anæsthetics, for instance, were more soluble in acid, but more effective in alkaline solution. It had been found that the tendency was for patients to put tablets of amethocaine under the tongue thereby anæsthetising the wrong part of the mouth. That difficulty had, however, partially been overcome by the introduction of chewing gum containing the medicament. That proved satisfactory until a patient aspirated the gum into the trachea. Medicated lollipops had since been adopted with satisfactory results. He was interested in the reference to the effect of vanillin in disguising the taste of chloramphenicol because, so far as he was concerned, no success had been obtained in the search for a specific taste antagonist. On the subject of preparing controls for clinical trials, the formulation of white tablets without special taste was easy, but controls for procaine, penicillin and cortisone had caused some difficulty. For these absorbable starch in suspension gave good inactive control preparations. A satisfactory control for thyroid tablets was obtained by using a coloured tablet containing sodium chloride and peptone.

MR. V. REED (London) expressed concern about the methods which many pharmacists, especially the younger generation, were adopting in dispensing under the National Health Service, and quoted instances in his own experience as a locum.

MR. H. S. GRAINGER (Westminster) drew attention to a recent publication in the British Journal of Radiology on the effect of various excipients used in barium sulphate suspensions on the subsequent X-ray picture. The washing of the barium sulphate free from electrolyte was, he considered, important as also was the degree of agglomeration of the particles. It was necessary to break down to the ultimate particle size before the effects of added viscosity could be considered. Chloramphenicol was

rendered palatable for children by incorporating it with synthetic chocolate.

MISS M. C. ISLIP (London) pointed out that doctors did not always want children's mixtures to be palatable as, for example, when bitters were prescribed to stimulate the appetite. She agreed with Mr. Hudson that there was always the danger of overdosage where potent preparations were made too palatable and, in any case, it was her experience that children themselves did not like highly flavoured mixtures when taken for long periods.

MR. G. R. A. SHORT (London) said that, although the flavour of cod-liver oil was best masked in emulsion, male fern extract could not be masked in that way or by the addition of flavouring. In an emulsion the surface area of the obnoxious material was increased. On the question of flavours generally, lemon and orange syrups were unstable and readily oxidised on storage. A difficult problem arose in connection with the aldehyde content of most flavours as it was not certain whether small amounts present were harmful to vitamin B and similar preparations. The use of boiled sugar lollipops was most interesting, and it was not difficult to envisage a great future for the iced lollipop, possibly in tonsillectomy.

MR. J. C. HANBURY (Ware) said that in the past the pharmacist had been concerned with the treatment of symptoms, but that at the present and increasingly in the future the bias was shifting first to prevention, second to cure, and only a very poor third to the treatment of symptoms. From the papers it was clear that pharmaceutical formulation was becoming daily more complex and inevitably more costly. The National Formulary and the Codex were still cluttered up with drugs of little or no value. Progress in pharmacy had become increasingly a matter of collaboration between the chemist and the pharmacist as also between the pharmacologist and the pharmacist. The B.P. was becoming increasingly concerned with proprietary materials, and he was of the opinion that resort should be made to the use of such materials where they provided a definite therapeutic advance.

MR. J. H. OAKLEY (London) expressed concern at the difficulties involved in translating formulæ intended for small-scale production to that of the large-scale manufacturing process. A facet of formulation which could sometimes be disturbing was the refusal of the Customs and Excise authorities to refund duty paid on spirit used in making preparations when they were of the opinion that the spirit had been insufficiently denatured.

DR. H. DAVIS (London) said he hoped that all the contractors to the National Health Service throughout the country would take note of many of the modern aspects of formulation which had been referred to in the papers.

MR. J. R. ELLIOTT (London) suggested that greater use could be made of effervescent granules and carbon dioxide water for the administration of medicines. Large quantities of inorganic potassium salts, chloride phosphate and citrate, had recently been found to be unacceptable in

mixture form, but that difficulty was overcome by converting them to effervescent granules. A satisfactory green colouring had been made by addition of minute traces of methylene blue to Liquor Tartrazini An imitation sarsaparilla flavour suggested in the Adelaide Children's Hospital Pharmacopœia was suitable for masking the bitter taste of alkaloidal salts.

MR. L. CASHEN (London) referred to the lack of availability of newly developed drugs except in compounded forms supplied by the manufacturers of the drugs.

MISS D. JONES (London) described an ointment prepared with equal parts of wool fat and a proprietary ointment containing titanium dioxide and 1 per cent. of brilliant green the colour of which rapidly faded, assuming a putty colour at the end of a fortnight. Substitution of soft paraffin for wool fat resulted in an ointment which retained its colour. Propylene glycol was not recommended as a vehicle for the administration of antibiotics; she had however been called upon to supply a 10 per cent. aureomycin solution in propylene glycol but had been unable to obtain any information about its stability.

DR. A. H. COOK (London) suggested that it might possibly be advantageous if a central body could be established to direct and correlate the large amount of extemporaneous research that was proceeding.

MR. F. W. BYRON (Nottingham) urged that more latitude be allowed in official monographs in regard to the inclusion of stabilisers. The U.S.P. had an omnibus clause permitting the use of stabilisers which in his experience were required in many preparations for export and he suggested that that lead might well be followed in the B.P.

MR. A. G. FISHBURN (Manchester) emphasised that formulation was the pharmacist's natural field of research. The problem could be divided into three main branches. First was the modification and improvement of existing products. Second was the more speculative type of work which required the development of new modes of pharmaceutical presentation. The third branch was investigation involving the translation of laboratory scale formulæ to a manufacturing scale.

MR. R. W. GILLHAM (Leeds) referred to the use of polyethylene glycols in the formulation of penicillin and sulphathiazole which had been found to be satisfactory. Referring to Mr. Eastland's observation that suppositories of polyethylene glycols were not always readily absorbed, it would be interesting to know whether those tested contained water, as he understood that the inclusion of 10 per cent. of water was advisable. Sulphathiazole was completely soluble in warm aqueous solutions of carbowax, the solution forming a gel on cooling. The same material had been used in veterinary practice for the treatment of mammitis. He briefly described experiences in dealing with a prescription for benzocaine emulsion which had given rise to misgivings on account of the numbness produced when taken by mouth. He criticised A.B.C. liniment and oily calamine lotion on the grounds that they were pharmaceutically inelegant.

DR. K. BULLOCK (Manchester) said that the physical chemist should temper his enthusiasm by reflection on biological facts. The laws relating to such matters as vapour pressure, osmotic pressure, freezing-point and boiling-point were based upon observations with non-living membranes and care was therefore necessary in the application of those laws in relation to living tissue. He had tried various concentrations of sodium chloride and concluded that all seriously damaged red blood corpuscles. He also referred to a published report which showed that sodium chloride had an irritant action in cerebrospinal fluid.

MR. R. L. STEPHENS (London) said that it had been pointed out in the literature that penicillin decomposed rapidly in polyethylene glycol, and Stephenson and Humphreys-Jones showed that tablets of glyceryl trinitrate in polyethylene glycol 4000 decomposed rapidly. In view of these facts, he was of the opinion that extemporaneous preparations of new medicaments should be formulated with established substances until more was known of their stability in newer bases.

MR. RAINE (London) pointed out that emulsion of benzocaine was another name for a paint of benzocaine included in the Formulary of Brompton Hospital and that it was used as an anæsthetic for the larynx.

MR. E. SAVILLE PECK, who rose amid applause, said that it was almost 50 years ago to the day when he accepted the responsibility of the Honorary Secretaryship of the Conference. He recalled with pleasure the happy times he had spent visiting and inspecting schools of pharmacy up and down the country, and during the Conference he had met many of those who co-operated in that work. It was often considered that figures such as Martindale and Glyn-Jones were the giants of pharmacy, but from the discussions he gained the impression that they were not alone and that the present era could also produce its giants. It would, he continued, be a great pity if the remarks made earlier by Mr. Reed were allowed to go out as the general opinion of the Conference. Accidents and mistakes were a great rarity, and the statement made by Mr. Reed should not be accepted by the Conference. Mr. Saville Peck said he recognised the need for close co-operation with the pharmacologist, but that was difficult for the retail pharmacist who, nevertheless, was able and should co-operate with the general practitioner. Referring to Miss Islip's remarks concerning palatability, he was interested in the action of valerianates as some preparations were odourless, and he was of the opinion that the smell was responsible for the effect. On the subject of tablets he drew attention to the fact that unless disintegration was rapid, there might be some local action on the mucous membrane of the alimentary canal.

MR. EASTLAND, in reply, suggested with reference to the drying out of jellies with cellulose derivatives that triethanolamine ricinoleate be tried if it were compatible. Claims had recently been made for the use of polyphosphates such as sodium hexametaphosphate in the preparation of contact lens solutions. With the use of such solutions the contact lens could be worn all day without discomfort. It was not his intention to

exclude ethyl oleate as a solvent for injections, but he had endeavoured to emphasise that further information on the partition coefficients of oils and esters was necessary as they affected the rate of release of the drug. In the preparation of barium sulphate suspensions it was important that the suspending agent should not precipitate mucin from the layer covering the mucous membrane as that would tend to bring about agglomeration of the barium sulphate. As to the difficulty with brilliant green in the presence of lanolin, he suggested washing with a phosphate buffer.

MR. NIXON, in reply, said he was interested in the standardisation of products, but pointed out that it was difficult to get reproducable results when dealing with proprietary materials. Limitations of dispensed products were difficult to define. Literature was not always readily available and he therefore welcomed the suggestion of a central office where information would be accessible to every pharmacist.

MR. SWALLOW, in reply, said that he agreed with certain speakers that pharmaceutical elegance was not always compatible with clinical efficiency. In his view the hospital pharmacist should make his formulæ as simple as possible and should not use new products if old ones would do.

MR. HUDSON, in reply, maintained that the tonicity of 1·4 per cent. sodium chloride ascribed to lachrymal secretion was in fact the tonicity of the exudate, and in all probability that was precisely the reason for the tear being spontaneously exuded from the eye. The viscosity of an emulsion played an important part in masking the flavour of unpleasant oils but, if too high, would itself cause unpleasantness. He agreed with Mr. Hanbury that the formularies were cluttered up with relatively useless drugs, but it was important to realise that they must cater not only for the acute sick, but also for people who were not well but had no specific condition. Effervescent preparations were not dead and still remained a useful and palatable method of administration. No doubt suppositories of chloramphenicol would appear from trade sources, but to be active 5 times the dose would be necessary.