REPORT OF A SYMPOSIUM ON THE STORAGE OF DRUGS AND MEDICINES

A SYMPOSIUM Session was held on Friday, September 16, 1949, at 9.30 a.m. Dr. Norman Evers, Chairman of the Conference, presided, and the opening speakers were Dr. T. E. Wallis, Mr. L. H. Boardman and Mr. J. B. Lloyd.

DR. WALLIS said that storage must be considered in relation to the various departments of pharmaceutical practice, viz.: (1) cultivation of vegetable drugs, (2) wholesale dealing, (3) hospital practice, (4) retail trade. The same commodity will often receive different treatment in the various circumstances, but in all of them the fundamental factors affecting the stored materials are the same. Special conditions arise from the nature of the premises and facilities peculiar to the different types of organisation. To fill in the details relevant to storage in the different circumstances one must, therefore, rely for information upon the experience of those pharmacists who are familiar respectively with the collecting and drying of crude drugs, with large warehouses, with the stock-rooms of hospitals, with the fitments of retail premises, or the packaging of goods for distribution.

Environment. The features of the environment which have a definite influence upon deterioration and storage are the following:—1. Atmospheric humidity; 2. Temperature; 3. Light; 4. Oxygen of the air; 5. Living agents of destruction; 6. Odorous commodities. Of all those factors, humidity and temperature appear to be the most important, since they not only have a direct and independent influence upon storage, but they also very largely govern the development of the numerous destructive living agents which abound everywhere.

Atmospheric Humidity. Moisture in the atmosphere is generally expressed in terms of humidity. When the atmosphere is completely saturated, the humidity is 100 per cent., when half saturated 50 per cent. and so on. If the humidity is over 75 per cent. it becomes dangerous in relation to storage. Under such conditions moisture is readily absorbed by certain chemical substances such as strong sulphuric acid, absolute alcohol, calcium chloride and salts of penicillin; moisture is also absorbed by some crude drugs such as squill, gelatin, gentian and digitalis. Some of the chemical substances, such as strong sulphuric acid and calcium chloride, will continue to absorb moisture until no more is present. On the other hand, when the humidity is low, water tends to be lost by some substances, such as crystalline borax, sodium carbonate and sodium phosphate, which contain a large proportion of water of crystallisation.

Moisture in the atmosphere is to some extent dependent upon the nature of the soil upon which the premises are built. A clay soil retains much moisture, whereas sandy soils lose moisture rapidly by drainage and, being non-colloidal, they do not tend to retain much moisture in loose association with the particles of the soil as usually occurs in a clay soil. Where underground cellars are used for storing stock, these considerations assume a major importance.

Temperature. Temperature may produce effects by itself; more frequently, however, its action is associated with other features of the environment. As pointed out by Savage in 1934, absorbent cotton wool is subject to deterioration by heat alone; a raised temperature leads to a gradual loss of absorbency, due to the effect of heat in promoting a reorientation of the molecules of fatty acid present in the infinitesimal residue of cuticle left on the hairs after processing; eventually the cotton wool becomes entirely non-absorbent. For general storage, an ideal temperature is about 55° to 65°F. (10° to 14·5°C.) which, being slightly higher than the normal temperature for a great part of the year and being maintained constant day and night, reduces the humidity and minimises the risk of sudden changes of humidity. Materials so stored therefore remain dry and tendency to attack by vegetable and animal organisms is greatly reduced, because these organisms cannot exist and multiply without sufficient moisture. For certain substances which are liable at ordinary temperatures to molecular change, such as insulin, penicillin, vaccines and antibiotics generally, storage in a refrigerator is necessary. When large refrigerators are available many drugs, such as ginger and chamomile, which are specially subject to bacterial or insect attack, may be successfully stored for long periods at the low temperature provided.

Moisture and temperature together have a combined effect upon the premises and upon the materials stored in them. For example, air at 9°C. (48°F.) contained 8·7 mg. of moisture per litre, when saturated, whereas it requires twice as much moisture (viz., 17·15 mg.) to saturate one litre of air at 20°C. (68°F.). Marked changes of temperature occur with the alternation of day and night, as well as with more occasional sudden seasonal changes. If, then, there is a sudden change in temperature from 20°C. to 9°C., as when moist warm air from outside enters a cold room or house, the air becomes over-saturated and half the moisture present is thrown out in the form of water. This water is condensed upon the walls and ceilings as well as upon the contents of the room and consequently the walls stream with moisture.

Light. Exposure to sunlight will remove the colouring-matter from many drugs, especially from those which contain chlorophyll, such as leaves and herbs in general, and also from petals of flowers which contain anthocyanin pigments or coloured plastids. This loss of colour is obvious, but other changes are induced which are not visible to the eye and sensitive constituents such as the glycosides of digitalis, may be destroyed. The vitamins as a group are sensitive to light, exposure to which ultimately leads to their destruction. The active constituents of rhubarb are orange yellow in colour and gradually change under the influence of light to a pinkish tint, giving visual evidence of deterioration. Several colourless substances acquire colour by exposure to light; santonin becomes at first yellow and gradually deepens in colour till it is almost black; silver nitrate also rapidly darkens in colour and phenol gradually becomes pink.

Oxygen of the Air. Oxidation of many active principles is brought about by atmospheric oxygen, as exemplified by the resinification of

the cannabinol of Indian hemp and the gradual loss of solubility in light petroleum of the abietic acids of colophony. Linseed oil and many volatile oils, notably oils of lemon and turpentine, resinify by exposure to the air, owing to oxidation effects. Cod-liver oil contains unsaturated fatty acids which break down by the action of oxygen causing both rancidity and resinification of the oil.

Living Agents of Destruction. Moisture, temperature and oxygen together encourage the development of many living organisms which feed upon the substances stored. Moulds of various kinds are the most important vegetable organisms and animal pests include mites, silver fishes, moths, ants, small beetles and cockroaches. The most important factor in controlling all these living organisms is moisture, for without sufficient moisture protoplasm cannot retain its life and activity. A low temperature, in the neighbourhood of 0°C., is useful to prevent the development of organisms from spores and eggs, but it does not usually destroy them. The most effective means of dealing with rats and mice is to make the store proof against their entrance into it; for example, avoid wooden floors, ceilings and roofs.

Odorous Commodities. Substances such as valerian, garlic and highly perfumed soaps must be separated from one another and also from other materials in such a way as to prevent the communication of odours.

General Rules for Storage. The principal items to which attention must be directed are the following:—1. Construction of the store-room or premises; 2. Protection from dust; 3. Shelving and its arrangement; 4. Packaging; 5. Inflammable substances.

Construction of the Store-room of Premises. In general, rooms should have concrete floors and rounded corners; any crevices should be filled in with cement. Wooden plank floors should be avoided chiefly because of the number of cracks and crevices where organisms could multiply. Wooden flooring is also open to penetration by rats and mice. An equable temperature should be provided, usually cool; this is one reason why a dry cellar is often a good location for a store.

Protection from Dust. Dust contains numerous spores and small living organisms, which under favourable conditions will lead to the infestation of the stores. Dust must, therefore, be excluded as far as possible so as to avoid contamination from outside, and in this connection packing-rooms should be separate from the store. Packing materials such as straw, hay, shavings and paper should not be in or near the store; bags and sacks should also be kept outside the store. Dust also collects in the crevices and upon the ledges, grooves and guards of machinery. Machines used intermittently must not be left about in a dirty condition.

Shelving and its Arrangement. Stacks of shelving should be kept away from the walls; the lowest shelf being about 1 foot from the floor and the highest 3 feet from the ceiling. This avoids contact with condensed water streaming down walls, from moisture upon the floor and from hot moist air near the ceilings. Island stacks of shelving kept away from the walls are to be preferred to shelving actually against the walls.

Packaging and Containers. Bags and sacks should be sterilised by some process such as heating to 150°F. (65°C.) for 3 or 4 hours or by thorough washing; when filled with vegetable drugs, etc., they should be kept off the floor on a staging of slats, or they can be hung from hooks. Packages must be well closed and made of materials resistant to attack by insects and other destructive animals. Paper wrappings must be closely folded and sufficiently tightly closed to exclude moths and beetles seeking places to lay their eggs. Where the store permits access of sunlight, opaque or amber-glass containers must be used when light is deleterious to the contents.

Inflammable Substances and Poisons. Inflammable substances must be kept in a separate store well away from the main buildings. Poisons must be stored so as to comply with the regulations of the relevant legal enactments.

Control of Pests and Sterilisation of Premises. If premises or goods become infected with vegetable or animal pests, means of control and sterilisation must be adopted. It is better, however, to remember and act upon the old proverb that " prevention is better than cure."

Storage, the Pharmacopœia and the Codex. The 1948 British Pharmacopœia places increased emphasis upon the storage of drugs and chemicals, for many of which it gives instructions about storage expressed in general terms. There is also the new requirement that " vegetable drugs are required to be free from insects and other animal matter and from animal excreta." A further item to be noticed is that storage over a long period results in the deterioration of many substances having a complex molecular structure, and in certain instances, such as for some of the vaccines, the period of storage is prescribed, usually in relation also to temperature. Requirements similar to those of the British Pharmacopœia will also be appended to many of the monographs of the new British Pharmaceutical Codex.

MR. L. H. BOARDMAN said that the storage conditions laid down by the British Pharmacopœia had proved satisfactory in practice. From the manufacturer's point of view, however, storage of galenicals and pharmaceuticals covered a very wide variety of subjects.

He proposed to deal with the matter under three main headings: (1) general conditions; (2) bulk containers; (3) small containers.

1. *General Conditions.* Structure of the warehouse or factory. The drug industry includes many types of operations and utilises a great variety of basic materials, and these inherent factors within the industry should have a distinct influence upon the conditions under which drugs are stored. The most important sources of outside contamination are: (a) rodents; (b) insects, flies, cockroaches, weevils, beetles, etc.; (c) general uncleanliness, from storage bins, accumulation of dust, etc.

(a) Drugs such as cascara, liquorice, senega, senna, etc., are usually stored as received and the term " good housekeeping," so popular to-day, should be ever in the minds of those responsible for the storage of raw drugs. In modern buildings, concrete, brick and steel will usually prevent

rodents, but with older buildings every effort should be made to seal all the entries, through pipes, etc., with wire mesh, and basements should be well lighted and have no dead spaces between walls, floors, etc. A regular system of pest destruction by means of a virus preparation should be undertaken as it is practically impossible to prevent access of rodents at some time or other.

(b) Prevention of insect contamination is not easy, but cleanliness of the walls and floors and the use of a mixture of pyrethrum and D.D.T., will eliminate most insect life.

(c) Other sources of contamination are the moulds, yeasts and various bacteria, and here proper sanitation in manufacturing and packaging and proper control of the manufacturing plant and the use of clean equipment will do much to prevent contamination. For storing smaller items and powdered drugs, metal bins of stainless steel, galvanised iron or black metal, with well-fitting lids, are quite suitable and preferable to wood bins. Ergot may prove difficult to store for a lengthy period, also figs and prunes which are only allocated once a year. In these cases metal bins with tight-fitting lids and the application of chloroform have proved satisfactory; also suspending a bottle of chloroform in a bin will usually maintain these drugs in good condition. Air-conditioning and the use of ozonisers are also worthy of mention.

2. *Bulk Containers.* Galenicals may be stored in bulk containers of various materials, the chief of which are wood, stainless steel, nickel, aluminium, galvanised iron and stoneware and glass-lined steel. Wood is quite good for storing many galenicals, oak being very suitable. Casks up to 200 gallons capacity can be handled fairly easily, they stand a lot of knocking about, they can be fairly easily cleaned by treating with calcium bisulphite and hydrochloric acid followed by washing and steaming. Such containers are suitable for storage of certain liquid extracts and infusions, where the alcohol content is low. Once the cask is conditioned it can be kept in use for many years for the same galenical. Stainless steel and pure electrolytic nickel make excellent storage vessels particularly for tinctures where the alcohol content is high and everything possible must be done to minimise loss. Following some years' experience it is possible to say that with alcoholic tinctures containing 60 to 70 per cent. spirit, the loss of alcohol averages about 2 per cent. when stored in wood.

There are many varieties of stainless steel, and galenicals over long periods attack some of them; or at least the appearance, aroma and flavour of the galenical is materially altered. Preparations containing methyl salicylate slowly turn pink. Oxymel of squill darkens in colour and the flavour alters; similar remarks apply to other preparations containing acetic acid. Ammoniated tincture of quinine does not keep satisfactorily. A preparation containing ammonium carbonate and senega darkens considerably and the flavour alters. These remarks apply only to a particular alloy of stainless steel which was found quite suitable for other galenicals, e.g., camphorated tincture of opium, compound syrup of glycerophosphates and compound tincture of benzoin. The particular brand of steel must be tried out over a period of time. Pure electro-

lytic nickel is suitable for tincture of belladonna, tincture of digitalis, tincture of capsicum, tincture of nux vomica, tincture of opium, tincture of squill, tincture of ginger, liquid extract of ipecacuanha, tincture of orange, ammoniated tincture of quinine, cascara preparations and compound syrup of figs. Aluminium vessels are suitable for preparations containing methyl salicylate and for senna preparation. Stone tanks can make very useful storage vessels for large quantities of materials and acid-resisting asphalt can be used for caulking the seams. Such vessels are satisfactory for storing mildly acid preparations such as oxymel of squill and compound syrup of ferrous phosphate, and can be easily cleaned. Similarly, acid preparations can be kept in glass or earthenware, but care has to be exercised in handling. Probably the ideal containers are glass-lined metal tanks which can be used for almost any type of preparation except those which are strongly alkaline. They are easily cleaned, nevertheless they have to be handled with reasonable care, otherwise the lining chips and repairs are expensive. The initial cost is also heavy. For solid preparations such as ointments, creams and confections, stainless steel, galvanised iron or glazed earthenware is satisfactory.

Temperature of Storage. In practice a temperature of about 60°F. has proved satisfactory, but conditions can sometimes be varied with advantage, e.g., tincture of capsicum is best made and stored at a lower temperature, preferably between 30°F and 40°F. as this eliminates fatty matter which otherwise may deposit during cold weather.

Time of Storage. Most liquid galenicals tend to deposit over quite a long period, probably due to slow coagulation of colloidal matter. Senna preparations are prone to deposit over a period of many months even when filtered repeatedly. Compound syrup of glycerophosphates is another preparation which may deposit after filtration, this being considerably affected by temperature. At temperatures exceeding 90°F., calcium citrate may come down and induce other salts to come down with it. In general, galenicals should be stillaged for periods from 1 to 6 months in order to have them in the best condition. Even then different conditions in the shop can bring about changes and cause deposits.

Small Containers. In most cases glass is the substance of choice, but many other materials are being used, such as aluminium (for tablets), plastic materials (for tubes and other screw-type containers), waxed board with screw caps (for ointments and confections), and metal tubes of pure tin or tin-coated lead and aluminium. For reagent bottles the use of polyethylene is being recommended and used particularly in America. Polyethylene is said to be resistant to all acids and alkalis up to temperatures of 160°F. and many organic solvents at temperatures up to 125°F. There is, of course, much less risk from the point of view of breakage. Pure aluminium containers, preferably anodised, are also being recommended as suitable containers for concentrated hydrogen peroxide, stabilised by the addition of about 4 p.p.m. of sodium stannate or sodium pyrophosphate. Pure tin tubes are satisfactory for almost all ointments and such articles as ichthammol and emulsion base oint-

ments. A cheaper tube is made from tin-coated lead, but as the tin coating is not always evenly applied pitting may occur and corrosion set up with subsequent damage to the contents of the tube. Aluminium tubes are not always satisfactory, particularly with certain emulsion bases of the saturated fatty alcohol type. Lengthy shelf tests under varying conditions should be carried out before finally adopting tin-coated lead tubes or aluminium.

Although it may not be difficult to find a suitable container for small packs and to add a suitable preservative it is not always easy to obtain a suitable closure and liner to prevent possible chemical effect on the liner and cap and also to prevent fungoid growth on the liner due to alternate evaporation and condensation. Moulded caps of synthetic resin are better than enamelled metal closures. The latter frequently become scratched and also rust. Metal closures are, however, cheaper than plastic, and metal is still the most widely used material for machine-made caps to fit machine-made bottles. They are usually made of tin-plate or aluminium. On the advent of the plastic cap the double shell metal cap with smooth external finish was introduced. Later the "Unishell" type was introduced with a considerable saving in weight, and the design of the cap prevented the wads from falling out and to a large extent overcame the difficulty of rusting. For pharmaceutical purposes, however, the plastic cap has much to recommend it as it is generally more elegant in appearance.

The following is a list of some of the liners available with notes on their suitability for various purposes.

(a) *Ceresine.* These wads are made from paper impregnated with linseed oil and combinations of certain gums and is frequently supplied with a combination cork backing. In general, ceresine liners are not recommended for preparations with a high water content as mould growth is likely to develop, but to prevent this a waxed composition cork backing can be used, the wax containing 0·25 per cent. of nipagin T. Ceresine liners are suitable for solvents such as alcohols, benzene or turpentine.

(b) *Blackol* liners are suitable for mildly alkaline products such as milk of magnesia and emulsions and will also stand up to liquid paraffin but are not suitable for benzene or turpentine or preparations containing them. Two other different liner facings are vinglite and whiteseal which stand up to stronger acids than ceresine.

(c) *Rubber.* This is recommended for strongly alkaline products such as ammonia; it is also suitable for hypochlorites and tincture of iodine and, when suitably treated, for penicillin and its solutions. Telecothene liners have also proved very successful for tincture of iodine in tests recently carried out over a period of several months.

(d) *Tin Foil* is used for liners on products containing spirits and volatile solvents which are difficult to seal with other liners. It is also useful for cosmetic creams containing water or volatile oils.

(e) *Alkathene.* These liners are obtainable in two forms, as the pure material or as a cork agglomerate, the latter being cork dust bound together with alkathene. This is probably the best form of wad as it has greater compressibility than pure alkathene and gives a better seal for most purposes. Alkathene itself stands up to all the strong acids and is insoluble in most solvents at room temperature. Alcohol and chlorinated hydrocarbons cause some embrittlement on exposure to bright sunlight under tropical conditions. Alkathene is resistant to caustic alkali and offers complete resistance to mould growth and attack by bacteria. Solid polythene wads are useful for volatile solvents such as nail varnish. Chemically alkathene is the same as polyethylene or polythene made by catalytic polymerisation of ethylene under pressure.

For many purposes ordinary cork has much to recommend it and waxed corks are suitable for emulsions in bulk. Pulpboard and waxed paper discs are also suitable for viscous pastes, tablets and most dry products. Many tablets are, however, packed nowadays for retail sale in special envelopes, particularly for export, using plastic film such as polythene or metal foil. Subaseal rubber caps are finding increasing use both for carboys and smaller containers, particularly for mildly alkaline products such as mixture of magnesium hydroxide. All articles should be shelf tested under varying conditions for periods of 3 to 6 months.

Sodium benzoate in 1 to 1·5 per cent. solution will prevent corrosion of many metals, and metal objects wrapped in paper or cloth containing 2 to 2·5 per cent. of sodium benzoate are protected; for example, steel, copper, brass, and soldered points; in the case of aluminium, pitting is prevented. Sodium benzoate incorporated into the adhesive prevents corrosion round the edges and underneath labels.

Liquid extract of cascara has been known to deposit after 6 months' storage at about 60°F. when the temperature is reduced by a few degrees. It is probably better to cool to about 40°F. and filter to obtain a liquid extract free from deposit. The B.P. note requires filtration after 48 hours; this is not sufficient time unless a particular temperature is specified. Liquid extract of ergot is also prone to deposit at low temperature; the British Pharmacopœia specifies that it should be kept at a low temperature and it is essential that the initial storage temperature should be low. The deposit does not appear to affect the ergotoxine content of the liquid extract. Tincture of capsicum frequently clouds and deposits at temperatures lower than 60°F. and should preferably be stored at as low a temperature as possible prior to sending out. Compound infusion of gentian may deposit after 3 months' storage when the temperature is slightly lowered; calcium tartrate has been found in the deposit and at other times crystals of hesperidin. Ethereal tincture of lobelia will also deposit a wax-like substance on exposure to cold. Simple linctus of the National Formulary may show in warm weather a semi-solid mass of crystals of invert sugar. A note regarding storage could, with advantage, be put in the N.F. Mixture of magnesium hydroxide B.P. has been found to take up both arsenic and lead when stored in certain types of bottle for periods up to 3 months.

The linctus of codeine of the National Formulary tends to ferment in hot weather, and the products of fermentation are very objectionable to taste and smell.

MR. J. B. LLOYD said that he proposed to view the subject from the standpoint of Storage in the Hospital Dispensary. In spite of the fact that the pharmacist is increasingly called upon to handle highly complex substances, many of which are inherently unstable, he thought that storage was less important than 20 years ago. The manufacturer endeavoured to produce preparations which would be stable under all possible conditions. Penicillin was perhaps the most unstable substance the pharmacist had ever been called upon to handle. For quite a time after the drug became available, it was common practice to send out injections in ice chests in order to minimise the loss of activity, but to-day it presented little or no storage problem. The material at present available could be stored at room temperature almost indefinitely; aqueous buffered injection solutions of penicillin-G could be stored at room temperature for at least 10 days, while still retaining at least 80 per cent. of their original activity. The stability of adrenaline solutions had undergone a similar improvement.

The use of preservatives and stabilising agents was not always a complete answer, as in many cases their use was, for one reason or another, undesirable. Moreover, storage often involved considerations other than the simple preservation of potency and strength. Provision must be made against contamination by dust and dirt; against chemical reaction between container and contents; against attack by insects and vermin and against reaction with atmospheric gases. Decomposition or infection by biological agencies may also have to be taken into account.

The store itself should be separate from the room in which actual dispensing was done. Adequate illumination, preferably natural, was important not only for its value in minimising mistakes due to the misreading of labels, but to keep down insect pests. Steel shelving and racking was preferable to the more usual timber. It was immune from attack by vermin, and did not provide a good foothold for climbing insects. More important, perhaps, was the fact that it is made in standard sections which may be added to at will, or transferred intact to an alternative site.

Conditions of temperature and humidity are much easier to lay down than to achieve in practice, adequate ventilation would, in general, be all that was necessary. Refrigerated storage space was, of course, required for antibiotic solutions or other biological materials. Inflammable liquids presented a serious fire risk, and statutory regulations must be observed.

Temperature was perhaps the most important factor. The higher it was the greater the velocity of chemical reaction and, within well-known limits, the growth of bacteria, moulds and yeasts. The new Pharmacopœia laid down storage conditions for quite a large range of materials.

Suitable conditions for all these substances were provided in an ordinary refrigerator. At the other end of the scale, solutions of protein hydrolysates for intravenous injection appeared to keep better at more elevated temperatures.

The Pharmacopœia was becoming increasingly concerned to specify the type of container in which substances were to be stored. Containers capable of excluding air, moisture or both were now frequently demanded, while the familiar "well-closed container" continued to be specified.

Glass was, of course, the traditional container for pharmaceuticals. Of its many advantages, not the least was that of transparency. The increasing use of parenteral solutions, however, had shown that it is not quite the inert material it was at one time thought to be, and had laid emphasis on its two principal failings, namely, its tendency to give off alkali to the contents, and the possibility of break-down with the separation of spicules. Quite recently a bottle had been submitted to him containing a solution of sodium bicarbonate which had been stored for several months, and from which a considerable quantity of glass spicules were filtered off. Had the bottle contained an opaque mixture requiring to be shaken, the consequences might have been serious. This breakdown was most apparent in containers which have undergone a heat sterilisation process, and was particularly evident in solutions of sodium citrate.

Free alkali given up to solutions from the container was provided for by an official limit test. The test, however, only applied to ampoules and similar containers of 0·5 to 25 ml. capacity. In his experience most ampoules available to-day passed the test, both on the whole ampoule and the crushed glass, but very few large containers passed when crushed. There was, in fact, no official specification for containers over 25 ml., although the United States Pharmacopœia applies a test of similar sensitivity to containers of all sizes. He suggested, therefore, that the test be extended in scope to containers of all sizes. Rubber wads, which also come into contact with the solution, varied considerably in quality, and here again an official standard would be of advantage.

Metals were rapidly coming into use as materials for containers. Distilled water stored for 12 hours in a stainless steel container had been found to have taken up lead, derived from the soldered joints. He had recently given a trial to an alloy, "Iconel," containing 80 per cent. of nickel, 14 per cent. of chromium and 6 per cent. of steel. It was more resistant to acids than monel, and seemed to offer possibilities as a bulk container for use during the preparation of large batches of sterile products. So far, he had not found any traces of heavy metals in a number of solutions stored for long periods. Like stainless steel, however, it was subject to attack by the halogens.

In these days of injections it was highly important that contamination from dust and dirt should be reduced to a minimum. From an examination of filter residues, it was apparent that many substances had

spent at least some portion of their existence in a hessian sack. For soluble substances, which were filtered during the process of preparing the injection, this did not matter a great deal, but in the case of insoluble powders it might present a serious risk. Would it not be possible for manufacturers to make a special " parenteral grade " ? Nothing more than B.P. standard of purity would normally be required, but care should be taken to see that contamination by foreign matter was reduced to the lowest possible level.

In the dispensary, dust cover stoppers should be used. Ointments presented a difficult problem, made worse by the traditional stone jar with paper cover, in which they are sent out by the wholesaler. A little reflection would bring to mind many instances in which packaging has made no progress during the last 50 years, and this in spite of the new and cheap materials which have become available. What was needed was a new approach to the problem. In the case of proprietary and branded goods, the incentives towards good packaging have produced remarkable results, but with the ordinary run of drugs, which will form the major portion of the stock of the dispensary while extemporaneous dispensing continues to exist, the position is not nearly so good. Some minor suggestions which quickly spring to mind are the packing of soft extracts, storax, caramel, etc., in collapsible tubes; the use of stoppers containing silica gel or other dehydrating material, and a host of similar ideas which in the proprietary field have become commonplace.

The CHAIRMAN, in inviting discussion, pointed out that the subject of preservatives had been discussed a year ago. It was impossible, of course, to separate preservatives entirely from the question of storage. Contributions from younger members would be particularly welcome.

MR. H. M. HIRST (Scarborough) had distinct recollections of John Whitfield, his chief nearly fifty years ago, coming to the shop in the morning and going straight to the powdered capsicum bottle and shaking it up. He himself still did that, because otherwise a mould would soon grow on the surface. In recent years it had become difficult to keep linseed meal since now it was wanted only once in three months. Glycerin and rose water would not develop a fungoid growth if made with glycerin of borax instead of glycerin. Why was compound syrup of glycerophosphates specially liable to develop mould? Points he had learned as an apprentice were never to refill a half empty bottle of sal volatile or ammoniated solution of quinine, and always to keep spirit of nitrous ether and hydrocyanic acid in inverted bottles. In many shops it would be impossible to carry out the suggestions which the opening speakers had made. Pyrethrum and D.D.T. mixed with derris was the ideal pesticide. Virus had been recommended for dealing with mice, but for mice and rats there was nothing to beat an old potato scooped out with arsenic in it.

For silver fishes sodium fluoride was best. For wasps carbon disulphide and carbon tetrachloride were better than the dangerous cyanide.

MR. A. W. BULL (Nottingham) agreed with Dr. Wallis that in many cases humidity associated with temperature was a potent source of deterioration. Where moisture could get in, i.e., where air could get in, with fluctuation of temperature there was a constant interchange of atmosphere over the stored material in the container, and therefore the more uniform the temperature of the warehouse or stockroom the less would be that atmospheric exchange and the better the storage conditions. Many packs which to all external appearances were perefectly sealed did in fact permit atmospheric interchange, and that might be responsible for deterioration due to chemical changes where moisture started the action, It might also be the cause of contamination by odour if the material was stored near to strongly-smelling articles. It was essential to choose the correct cap and lining disc and to apply them in an efficient manner. Certain plastic caps, particularly those of larger diameter, tended to become loose on storage more readily than metal caps of similar dimensions. Rubber might be the source of contamination with zinc. In large-scale manufacture many of the tanks were of 1000 gal. capacity and upwards. In addition to the inside of the tank all the external fittings should be thoroughly cleansed—the measuring gauges, valves, pumps and pipe-lines. It must be possible to take them to pieces in units which were easy to handle. Valve seatings should be examined regularly and replaced at intervals. Where large quantities of penicillin lozenges were produced they should be stored in a well-sealed container in an air-conditioned room and packaged under the same conditions.

MR. R. MAXWELL SAVAGE (Barnet) said that the deterioration in surgical dressings arose from the surface chemistry of the fibre, and in particular the orientation of the fatty matter which was present. Its occurrence in any particular sample of cotton wool was almost impossible to forecast. A sample which from analysis might be expected to deteriorate quickly might remain perfectly absorbent for 7 to 10 years, while another sample which seemed to be almost identical might change in a few months. A low temperature was better for storage. This problem was more troublesome in tropical climates than in temperate climates. There was probably sufficient scientific knowledge in existence to stop the trouble altogether, and the real barrier was commercial. Once the article was properly sterilised and packed it was likely to remain sterile. These articles were apt to accumulate dust, and if that happened it was not reasonable to expect the package still to retain its sterile condition when opened by the user.

MR J. H. OAKLEY (London) said that Lithcote, a plastic material, was very economical for some purposes which did not require high precision standards; it had the disadvantage of chipping readily, but with containers which were carefully handled it gave a satisfactory lining. The polythene type of plastic was easily sprayed on, and gave a satis-

factory lining. Initially it was more expensive than Lithcote, but less liable to chip. It was soft and readily scratched. Sprayed metal—a mild steel container sprayed with tin or stainless steel—had not proved quite so successful in practice as had seemed likely. Stainless steel was useful for a variety of preparations of different *p*H, alkaline or acid. Polish greatly influenced the non-reactiveness of the stainless steel. Many stainless steels rusted if they were not highly polished. A chemical reaction seemed to be set up which pitted the stainless steel, not only shortening the life of the vessel but also giving impurities to the products which were being mixed in the steel container. In the storage of galenicals, it was important that the preparations should be issued in chronological order. Plastic wads were not very resilient and the caps tended to become loose or did not form an effective seal.

MR. R. W. GILLHAM (Leeds) referred to the bulk packing of ointments. Earthenware pots and paper covers were untidy and difficult to manage and his firm had recently adopted waxed card containers. These were unsuitable for some types of ointment, such as those with aqueous bases and with volatile constituents like methyl salicylate, but in general they were satisfactory for ointments with paraffin bases. Ointment of yellow mercuric oxide that had been packed in waxed card containers had been found to discolour in sunlight. The darkening was found by experiment to be due to the blue end of the spectrum. The same thing occurred even with opal glass containers and they had to go back to the old-fashioned earthenware pot. If a parchment cover was used it let the light through and the ointment became discoloured. Another curious example of the effect of light was with a batch of liquid paraffin which developed a peculiar odour and taste and a pale straw colour. Many makes of rubber stopper were unsuitable for iodine bottles. Brushes having aluminium stems were unsuitable; the aluminium very rapidly combined with the iodine. Little had been said about strong smelling drugs. Infants' and invalids' foods stored in cardboard containers should be well segregated from strong-smelling drugs. Selling goods in the correct time order was very important. This was emphasised in the training of apprentices, but qualified pharmacists were not always free from blame. Sometimes drugs were returned as unsatisfactory and credit was asked for them, but the batch number showed that they were made 6 or 7 years before. The top fermentation which sometimes occurred in syrups was very troublesome. Originally the liquid might be strong enough in sugar to prevent fermentation, but evaporation from the top layer, followed by condensation, gradually weakened the top layer and moulds developed. One remedy was to shake the bottles every day, as Mr. Hirst suggested should be done with capsicum. A not very satisfactory remedy when there were thousands of bottles.

MR. T. D. WHITTET (London) urged manufacturers of soluble sulphonamides to issue them in brown containers. The effect of light seemed to apply to a number of drugs containing amino groups, such as tablets

containing ethylenediamine, *para*-aminosalicylic acid and some of the sulphones. Storage problems in hospitals were of two types, bulk storage and storage in wards. Mention should also be made of containers issued to patients. It was desirable to try as far as possible to get a uniform type of storage container for the wards, with adequate labelling. The out-patient dispensary frequently gave out drugs which were to be kept by the patient for a month, and sometimes longer. Generally they used waxed cardboard containers for ointments, and often for tablets. Some of the waxed cartons were not suitable for hydrous ointment and other oil-in-water preparations, and also, for many tablets, such as tablets of acetyl-β-methylcholine.

For bulk storage, mobile shelving (Rollstores) was particularly useful. It was possible to fill a whole storage room with lines of these mobile shelves as long as a gangway was left. Stainless steel metal bins on casters were very useful. They could be pushed under a section of the metal shelving, and wheeled out when wanted. It was possible to get behind them for cleaning and to prevent insects and so on. Uniformity of appearance of storage containers in the pharmacy itself was of importance. Tablet containers which resembled a book about the size of the B.P., with a space for a label, made it possible to store large quantities of tablets in a small space. They had found a series of metal trays very useful for ampoules and small proprietaries. Each tray would take a couple of boxes of a certain size of ampoule and could be labelled and put in a cupboard, where they were easily accessible. With regard to the question of standards for blood bottles, a committee had been set up three years ago and had held sporadic meetings. It was hoped to standardise ½-litre and 1-litre blood bottles, of the same height and neck dimensions, so as to have a standard bottle for any transfusion fluid. The trouble had been the glass itself.

MISS V. W. BURRELL (Pinner) said that in a great many cases discoloration on storage was due not only to adverse conditions of temperature, oxidation and moisture, but also to traces of heavy metals such as copper and iron. Ascorbic acid, aneurine hydrochloride and ethyl oleate were instances. Sometimes the connecting bends or screws used in stainless steel vessels were made of brass and not entirely stainless, and this could easily be overlooked. In solutions for injection, where the prevention of discolouration was important. Seitz pads were responsible for traces of iron and, particularly, of calcium which caused precipitation with ethanolamine oleate. Calcium and zinc from rubber stoppers caused turbidity. Polyvinyl chloride liners would withstand steaming. Polythene did not stand temperatures above 100°C.

MR. R. L. STEPHENS (Brighton) said that plastic caps made with wood flour as a filler absorbed water in high humidity and gave it off in low humidity, causing a dimensional change which might be as great as 4 per cent. and which was quite sufficient to cause loosening. In that respect, metal caps were superior and when using the latter it was necessary to

choose a pliable rubber wad which would allow for the change. Cork had been used but many alcoholic pharmaceutical preparations destroyed its resilience. Lithcote and other plastic materials had the advantage of cheapness, and although they did tend to chip easily they could be fairly readily repaired. Bakelite and Lithcote were thermosetting plastics. Polyethylene as thermoplastic material is also known as Alkathene. Telcathene is the trade name for the Telegraph Construction and Maintenace Company's grade of polyethylene. Polythene was resistant to chemicals, but its resilience was not sufficient to counteract the movement of the cap, nor to take up the irregularities round the top of the bottle. It was useful for carboy stoppers and in the form of polythene film as a liner for metal boxes. Plasticised polyvinyl chloride loose liners could be used over and over again; they would keep out vermin, and would not contaminate the contents. Unplasticised polyvinyl chloride was a rigid material which would stand a temperature of about 80°C. Containers and tubes could be made from the rigid polyvinyl chloride. Plasticised polyvinyl chloride was available as tubing and had the advantage over rubber of being compounded from relatively simple materials, i.e., a single chemical which had been polymerised and a plasticiser which one could specify. For chemical purposes the plasticiser should be dioctyl phthalate, which had very little odour and was non-toxic. The material was resistant to tincture of iodine. Rubber hydrochoride had come on the market in the form of Pliofilm. A big advantage was that rubber hydrochloride was resistant to the passage of moisture vapour, whereas the other films let moisture vapour through very readily.

He had had considerable difficulty with the deterioration of the flavour and odour of liquid paraffin emulsions. Even when stored in amber containers these gave rise to an oily, rancid flavour and a strong odour. The emulsions of the B.P. and N.F. were particularly bad.

MR. J. A. MYERS (Bradford) said that most hospitals were steam heated, and steam flies came into almost every room. Dusting with pyrethrum, derris or D.D.T. was not the complete answer. Amber glass bottles were the most suitable containers for sterile solutions of sodium citrate, and he would like to ask whether there was any white glass which was resistant to sodium citrate and did not form spicules on autoclaving. Was there a cheap canister which could be recommended for ward storage of kaolin poultice? Cotton wool in the usual packets was not suitable for export. It was amazing that it should still be stored in blue paper packets, a most unsuitable container.

MR. H. S. GRAINGER (Westminster) said that Hysil flasks were best for citrate solutions. They did not last for a great many autoclavings, but they were far better than glass bottles. Recently they had had trouble with the rubber closures used for the ordinary M.R.C. blood bottle. The rubber caps were normally treated by boiling in sodium carbonate solution for a short time and then rinsing with distilled water after being treated with a chemical detergent. The amount of permanganate

required in the B.P. test for oxidisable matter increased about tenfold after the water had been autoclaved in contact with the rubber caps and with the rubber tubing used in the drip apparatus.

MR. R. H. HENRIKSEN (London) referred to recent experience with "surplus stock" cotton wool. It was in good physical condition, but had completely lost its absorbency. In similar cases of long storage he was sure that manufacturers would be very pleased to have material returned to them.

MR. S. CANNELL (Ashton-under-Lyme) said that he could confirm that water sterilised in containers closed with rubber caps no longer passed the B.P. test. Penicillin solutions which were passed through rubber tubing, as in a drip apparatus, lost potency, and if water sterilised in rubber capped bottles was used for the preparation of penicillin solutions they might deteriorate more rapidly.

MR. E. H. REID (Dagenham) asked whether Mr. Boardman had any experience of accelerated storage tests.

DR. W. MITCHELL (London) said that the remedy for silver fish was pyrethrum as a spray or aerosol. In general, pyrethrum was extremely valuable and, if it was applied as an insecticidal fog it penetrated into the crevices, but its effect was not persistent. Some drugs had a concealed infestation. Calabar beans could look quite sound and yet be empty. The ideal plant for handling and storage was glass-lined steel or enamelled cast-iron in conjunction with glass pipe-lines. It was expensive and it was necessary to be careful about the many gaskets used in the pipe-lines. More care was necessary when using stainless steel, which was the next best thing. One had to be careful that the fabricator did not solder the seams, and that the fitters, or even the maker of the plant, did not introduce zinc or lead washers or brass screws. Lithcoting was a valuable and cheap process and did not chip so badly as some people had suggested.

DR. G. E. FOSTER (Dartford) referred to labelling . It was very difficult to stick a label on a sheet tin container so that it would not come off. They had tried many glues and pastes, but had not been able to find one which was suitable.

MISS O. B. FLETCHER (London), referring to the difficulty of citrate solutions forming glass spicules, said she had found that a successful preventive was the addition of 0·05 per cent, of citric acid to the original solution.

DR. E. F. HERSANT (Dagenham), asked over what period the loss of alcohol had been 2 per cent. It was with the larger size of wide-mouth bottles that the loosening of plastic caps was most noticeable, and he thought that it was due to changes of temperature and the difference in the coefficient of expansion between the cap and the glass bottle. That was borne out by the fact that it was mostly in the tropics that these complaints arose.

MR. V. REED (London) said that paraffin emulsions, when stored in the shop, seemed to develop mould more rapidly than in the case of the emulsion with phenolphthalein. He would like to know whether pyrethrum lost its activity when stored in ordinary conditions, as in the shop round. Some chemists stored it in paper or cardboard cartons.

DR. J. M. ROWSON (London) said that his experience of the storage of many hundreds of drugs was that by far the best container was the ground glass stoppered jar. Museum jars containing highly susceptible vegetable drugs had retained their contents in good condition for a very long time. Next to that he would put the Bakelite capped bottle as exceedingly efficient, especially for powders. Waxed and brown paper coverings were very unsatisfactory. For the storage of crude drugs in ordinary drawers, he had had tin containers made in three sizes, with the largest size there were four tins in the drawer; the next size divided that longitudinally so as to get eight tins in, and the next, divided also traversely, got sixteen in. To prevent insect infestation in, for example, belladonna and henbane he put 1 ml. of chloroform into each container. Perspex containers were useful, particularly for museum demonstration purposes. It was a method of display that the retail pharmacist could use more.

MR. SPEAKMAN (Birmingham), in connection with kaolin poultice, said that the makers of antiphlogistine used to put it in aluminium containers, and one could get aluminium containers holding about 1 lb. quite cheaply. They had found that polyvinyl chloride protected rubber satisfactorily against oils for 6 months.

The CHAIRMAN said that not much had been said about fermentation, which, especially during the hot summer, had been most troublesome. Some yeasts would grow in very high concentrations of sugar, but the general cause was that mentioned by Mr. Gillham—condensation in the upper part of the container forming a dilute solution on the top of the liquid. Fermentation, however, might not always be caused by yeast, and they had had a case recently of its being caused by a bacterium in malt extract. The gas produced might not always be carbon dioxide. Some time ago they had a case of fermentation in a preparation of malt extract and hæmoglobin which was caused by nitrogen-producing organisms. Rubber caps were made from an extraordinary variety of ingredients, the rubber content varying from about 20 per cent. up to nearly pure rubber, and the manufacturers were very secretive about what they put in.

DR. T. E. WALLIS, replying to the discussion, said that penetration of bags by dust, due to variations of temperature, was an important point. Museum cases were usually made "dustproof" (so called). They had some in the Society's Museum, and found that when central heating was introduced they became particularly inefficient. One of the main reasons for that was, he thought, that there was a much greater alteration in temperature inside the cases, which resulted in small currents of air going through exceedingly small cracks and producing a deposit of very

fine dust over everything, which was difficult to deal with. He thought that the reference by Mr. Whittet to steel shelving and steel containers, provided a very useful hint on how some pharmacists could considerably improve their storage conditions. He would associate with that the remarks of Dr. Rowson about the storage of drugs in tins as one of the best ways of keeping insect pests away from specimens. Storage of things like starch and chamomile in open drawers in shops was quite common, and caused deterioration. Dust and moisture got in and led to a good deal of spoilage of stock. The most important precaution to take against silver fish was to keep the place absolutely clean, and if they were found, empty the place out and whitewash it. That was an old-fashioned remedy, but it was quite a good one.

MR. L. H. BOARDMAN, who also replied, said that wood floors could always be covered with acid-resisting asphalt, which made a very satisfactory surface. Humidity and temperature were the most important factors. He thought that 60 per cent. humidity was a fairly reasonable figure to work to. Ozonisers were useful to eliminate smells; they had tried them recently and found them very satisfactory. They too had found that plastic caps tended to become loose more than metal caps, and he thanked Mr. Stephens for his explanation. It was no use buying a stainless steel tank for storage purposes unless it was welded with the material of which the tank was made. If they were soldered, they were not stainless steel tanks.

Some types of rubber stoppers had proved satisfactory for tincture of iodine over 4 to 6 months. They had found Telcathene very satisfactory, and better than anything else so far. He had not had any experience of spraying metals except for repairing copper pans, and he had not been very satisfied. He always asked for stainless steel containers rough polished or smooth polished, as the case might be. He was not sure that that was the answer to the problem of keeping these in good condition and helping the storage, but it might be part of the answer. Galenicals were always sent out in chronological order, and that was very important. If old stocks were found in the pharmacy he did not think that any blame could be attached to the manufacturer or wholesaler. Polythene and cork dust made good liners, because they were more resilient that the polythenes themselves. They had found in the past that mercuric oxide from various makers discoloured, traces of metals probably catalysing the change. They had never found liquid paraffin to go wrong, but there was no doubt that the emulsion of the N.F. did go off very quickly, and in his opinion it had not nearly enough preservative in it. The B.P. emulsion contained two preservatives, and in a much bigger proportion than that of the N.F.

He recounted an experience of spontaneous chemical reaction in some tablets of ammonium chloride and sodium nitrate when packed in a large waxed container. He would like to thank Mr. Stephens for his excellent discourse on plastics, from which he had obtained quite a few hints. Dr. Mitchell spoke highly of pyrethrum. It did not last for long, but the

knock-down effect was tremendous. When mixed with D.D.T. he had found it perfectly satisfactory without the addition of derris, which was not pleasant to handle in bulk, particularly in powdered form. A material called Tinol was very suitable for getting labels to stick on tins. The loss of alcohol to which he had referred was 2 per cent. in 12 months. Pyrethrum lost activity on storage. Ground glass stoppered jars were very good containers for drugs, but rather expensive.

MR. J. B. LLOYD, also replying, said that by the use of the mobile type of metal shelving they had been able to increase their storage capacity about 6 times for the space available. New containers should be used in replacements for wards. A standard, or several standards, for glass containers for pharmaceuticals and foods was highly desirable. The use of acid salts had done a great deal to cut down the occurrence of glass spicules in citrate solutions. Water from a glass still with double distillation, passing through a piece of rubber tube not more than 1 foot long, had failed to satisfy the B.P. test for readily oxidisable matter. That seemed to be a general failing in distilled water which came into contact with rubber. Aneurine hydrochloride solutions were particularly liable to deterioration, and after long storage a brown precipitate might occur.

The CHAIRMAN commented on the very wide range of the subjects discussed. There were still quite a number of aspects which had hardly been mentioned. The question of tropical storage, for instance, in these days of export. This was very important to manufacturers. The symposium had been not the least successful of those which had been held up to date, and he would like to thank first of all the three opening speakers for their excellent introduction and then all those who had contributed to the discussion.