PHARMACEUTICAL ASPECTS OF GLASS AND RUBBER

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Glass

For many years pharmacists have been "glass conscious" and aware of the necessity of controlling its quality and characteristics when glass containers are used for pharmaceutical preparations. Thus the B.P. 1898 specifies lead-free bottles for solutions of ammonium acetate and citrate and green glass for solution of potassium hydroxide, and in our records are such cases as the extraction of arsenic by potassium carbonate from its glass container and the blackening of suspended bismuth salts by specks of sulphide on the surface of the glass. In recent years, however, we have found it necessary to take an even greater interest in glass because of the gradual introduction of drugs of very high potency, and consequently of small dosage, where regard must be paid to stability, because a small change in structure during a sterilisation process or during storage may mean a considerable drop in potency. Many of these new drugs are sensitive to change of *p*H and glass can so easily supply the means for this. This more critical attitude was reflected in the B.P. 1932 which, having introduced the modern types of parenteral injections, included control tests for the limit of soluble alkali in the glass containers used and specified those medicaments and preparations which should be packed in proved-glass containers. The official tests for the alkalinity of glass were interesting and have led to considerable controversy for there were two schools of thought. Two tests were devised: (*a*) the crushed glass (or interior) test and (*b*) the surface test. The crushed glass test was final, for any glass passing that test must also pass the surface test, but not necessarily *vice versa*. On the other hand it was urged that the surface test was a "practical" test because only the surface came into contact with the medicament. The tests were restricted to containers with capacities of 0·5 ml. to 25 ml. It did not appear logical to apply *both* tests for only the relatively expensive borosilicate glass would pass both tests whilst the cheaper soft soda-lime glass would rarely pass even the surface test. It is inevitable, of course, that economics should be important and the problem of control of the quality of glass will probably vary in different countries according to the availability of the raw materials. Thus, in Britain borosilicate glass is not in good supply. The problem, however, began to resolve itself by the introduction of the so-called "surface-treated" soda-lime glass whereby it is possible to produce on its surface a resistant skin of silica which will pass a surface test but not necessarily the "crushed glass" test. The glass technologists urged the adoption of this surface treated glass for containers, other than ampoules, when an alkali limit was essential. The B.P. 1953 has, in effect, done so; the "crushed" test has been deleted and a surface test retained, but without limitation to the capacity of vessels. I feel, however, that this surface-treated glass has been officially taken on trust for there are no published

data to show that the resistant skin has a satisfactory long life and will not break down and expose an alkali-yielding under surface.

I think it is desirable that we should have a durability of surface test for this glass, particularly as it will be used for large containers which, unlike ampoules, may be used over and over again.

There are also two schools of thought regarding the type of surface test. Both tests are based upon the same technique, the neutralisation of a limiting amount of hydrochloric acid. There is the method official in the Swiss Pharmacopœia which directs that the interior surface of the container be calculated and a quantity of standard acid + indicator per unit area of surface should be added. This ensures that the quality of the glass is tested and the size of the container is eliminated as a factor. On the other hand, the official B.P. test, which is similar in principle to that in the U.S.P., arranges for the container to be filled to its prescribed capacity with the standard acid + indicator solution. In this case the volume of the container is a factor in deciding the result, for if one compares the ratio of surface area to volume of standard acid, it is obvious that the small container will be subjected to a much more severe test than a large container, in fact, it could happen that with two containers made from the same glass but of different capacities, the small one may fail and the large one pass. This does appear to be illogical but the deciding argument advanced in its support is that it is a test of actual conditions to which an alkali-sensitive solution may be subjected.

At the moment we have focussed only on the possibility of alkali being yielded by glass but I would like to ask what other material is liable to be extracted. It would be well to be careful in this respect as we now deal with such sensitive medicaments and it may well be that traces of other metals may be important in the future. We have, for example, the question of glass containers for radio-active isotopes.

In addition to the alkali hazard there is also the very disturbing phenomenon of the flaking of glass from the surface of containers of citrates, tartrates and salines. We should be happier if we knew the cause and if we could have a control test which would exclude glass showing this tendency. The Pharmacopœia has no such test and can only warn that it is likely to happen. The result is generally obvious and detectable in solutions, but not with citrated blood.

It has been suggested that the interior surface of glass containers could with advantage be coated with a silicone forming a water repellant surface, thus preventing the extraction of alkali and the flaking of the glass.

Experiments carried out in The School of Pharmacy by Mr. P. J. Parr, in which silicone-treated bottles were tested against untreated controls showed that there was no protection against flaking.

In addition to the hazards of alkali and of flaking there is also the question of protection against light and the production of non-actinic glass. Pharmacopœias record increasing numbers of medicaments and preparations which are photo-sensitive but again there is little data published of the efficacy of coloured glass as a protecting agent. There is

a tendency against the use of coloured glass for injection-solutions because such glass tends to make it difficult to see the condition of the contents. I would agree that this factor is far more important than protection against light, which can easily be ensured by storage in a carton or cupboard. The same reasoning does not apply to solid photosensitive substances and it would be interesting to know if glass can give a complete protection.

Finally, there remains what might be termed the physical characteristics which we require in pharmaceutical glass and which the glass technologist must include in his considerations of quality. We must have ampoules which (*a*) will easily melt and seal, (*b*) will not splinter on opening, (*c*) contain no glass "powder." The presence of glass powder in ampoules is a hazard and can be avoided by care in manufacture. The subject is discussed in a review[1] and by Brewer and Dunning[2] who, contrary to accepted ideas, claim that the presence of such powder is not harmful. Nevertheless we must avoid it.

Rubber

Whilst it is probably true to say that we have the problems concerning pharmaceutical glass fairly well focussed it is far from being so in the case of rubber. This is because these problems are of more recent origin, coming into prominence with the advent of parenteral injections. Indeed, it is not until the 4th Addendum (1941) of the 1932 edition, that the British Pharmacopœia mentions rubber, and attempts some control of its quality and use as a closure for multiple-dose containers. Amongst the problems which this container presents is that of contact of the medicament with a rubber closure or cap, and it becomes of increasing importance, as our experience extends, to realise that rubber, like glass, may yield substances to a pharmaceutical preparation but in addition, unlike glass, it may extract substances.

It is only in recent years that we have begun to discuss these aspects of rubber. Thus[3] at the Fifth International Congress of Military Medicine and Pharmacy held in London in 1929, there was an extended discussion on glass and on rubber but the latter was viewed only from a rubber standards angle for catheters, gloves, tubing, etc., and no mention was made of its action on medicaments.

Again although rubber tubing is used in transfusion work the new B.S.I. standard for "Rubber Tubing for Hospital Use" (1882; 1952) is concerned solely with those factors such as storage and heat which may be harmful to rubber. No consideration whatever is given to the harmful effect which the rubber tubing may have on the solutions which have to pass through it or how these effects may be minimised or obviated by a specification of the quality of rubber. Such standards are of little value to the hospital pharmacist and it would appear that pharmaceutical opinion was not consulted when the standard was devised.

Rubber in the form of surgical rubber gloves may also be deemed of pharmaceutical interest as many hospital pharmacists are concerned with their purchase, storage, sterilisation and use. Yet again, the B.S.I.

standard for surgical rubber gloves (1803; 1952) is careful to list those factors which cause a deterioration of the rubber. Warning is given against antiseptics with an oil base but no regard is given to the effect of such substances as lysol which do not cause deterioration but which dissolve in the rubber creating a highly bactericidal surface.

All this emphasises the importance of bringing together the pharmacist and the rubber technologist for the mutual tabling of problems and ideas so as to get an understanding of what is wanted and how it may be obtained. How important this is is apparent when we record what we know already of the hazards of rubber, and in the following account I have attempted to create this picture.

At the outset it is important to realise what is meant by rubber, for it is quite apparent from Mr. Haworth's account and from our own experience that it is difficult to define it. Even a specified composition of the rubber-mix may give varying results. Therefore we can control it only by a general definition and control tests.

In 1937 I had occasion to examine a batch of injection of morphine hydrochloride (2·5 per cent.) containing 0·1 per cent. of chlorocresol, packed as 30 ml. quantities in bottles closed with black rubber caps which were wired on, presumably after autoclaving. The complaint was that there were black specks floating in the solution. The injection was nine months' old and had been out to the Near East. Examination easily showed that the black specks were flaked particles from the rubber, but in addition it was found that there was little or no chlorocresol in solution and consequently no bacteriostatic protection. Also the *p*H of the solution was about 2·5. The solution was sterile but the rubber had nearly perished. It was hard and would soon have cracked and admitted bacterial infection. The solution was quite colourless and had a full morphine content. Further tests showed that the rubber had extracted the chlorocresol and, being cold-cured rubber, had yielded an appreciable amount of hydrochloric acid to the solution, which had the effect of stabilising the morphine salt. Had another type of cap been used (freely available at the time) then it would have been possible for the *p*H to have risen to about 9·5 or 10·0 giving a short life to the injection.

It is this type of experience which shakes one's faith in rubber as a suitable material to bring into contact with medicaments, particularly when one contemplates the list of varied and highly active substances which are incorporated in a rubber mix. It seems too much to hope that all of them will be firmly anchored within the mass and never show their presence outside. There has not been a great deal of work done on the effects of rubber on pharmaceutical preparations and usually the workers have not defined the composition of the rubber which they have used and, therefore, it must be borne in mind when assessing the results that another type or batch of rubber might not produce the same effects.

In judging the quality of rubber for our purpose it may be convenient to consider it under the following headings.

(*a*) The physical characteristics. (*b*) The yielding of extractives to solutions or preparations. (*c*) The absorption of substances by the rubber

from the solution or preparation. (*d*) The effect of rubber on medicaments.

(*a*) *Physical Characteristics.*

During the last 15 to 20 years great advances have been made in the technology of rubber resulting in very remarkable changes in the physical characteristics of rubber, particularly with respect to ageing or perishing or oxidation. One has only to think of the old and the modern types of rubber hot-water bottle to realise this. One of the main problems in the old days was the short life of the rubber caps used for injection bottles which quickly went hard and cracked and then allowed leakage. It was quite usual to attempt to lengthen the life by varnishing or waxing the cap to protect it from the air. The waxing method was rather unpopular with the medical practitioner as it led to blocked needles. This is not necessary to-day as a modern rubber cap does not readily perish but can retain its characteristics over years.

Another character important in rubber caps is that consistency which permits the easy passage of a needle, and therefore minimises the blunting of the needle. Modern rubbers offer a big range in this property and one realises this in attempting to pierce a carbon-rubber designed for resistance to oil. When the needle is withdrawn another important characteristic of rubber should be apparent, namely elasticity causing an efficient blocking of the hole so that the cap can be repeatedly pierced without loss of protection of its contents. Elasticity and "piercibility" are not apparently synonymous. These and other characteristics of rubber in relation to rubber caps have been discussed elsewhere[4].

(*b*) *Extractives from Rubber.*

Pharmaceutical rubber, like glass or any other closure material must not alter the composition of the enclosed preparation either by reaction with it, by addition or by abstraction. It is important, for example, that if water for injection is enclosed it should, after processing and on storage, still comply with all the tests for water for injection. Extracted oxidisable matter, probably protein, has been reported by Grainger[5] as coming from rubber caps and confirmed by Lloyd[6] who also states that freshly distilled water passed through a piece of rubber tubing failed to pass the official test for readily oxidisable matter. Cooper[7] confirms this and also refers to extractive which gives a sulphide reaction with iodine and sodium azide.

Anticipating the possibility of water soluble extractives, the British Pharmacopœia, 1953, specifies that rubber caps shall be boiled in several changes of distilled water.

I understand that it is possible to obtain deproteinised raw rubber and the question arises why this type of rubber should not be specified for a pharmaceutical rubber mix. Would the cost be prohibitive or would a bottle-neck in supply be created? It is also of interest to note that the protein content of rubber is related to the power of absorption of water, which is an undesirable property as far as we are concerned, particularly

when packing moisture-sensitive material. Anyone interested in this aspect might care to read an account by Taylor and Kemp[8] where the factors governing the rate of absorption of water by rubber are discussed. Different kinds of rubber have different values for water absorption. It is apparently as important in insulation problems as it is with us.

Apart from protein, one must guard against the presence in rubber of such a filler as "whiting" which could react with solutions and medicaments of low *p*H and quickly inactivate some of them. This may be of great importance in biological preparations, such as insulin and pituitary. The almost inevitable presence of zinc in rubber can be a hazard. Ragznek[9] reports the effect of temperature and *p*H on the rate of leaching of zinc salts from rubber closures in contact with acid substances. These two papers are important and interesting in that the quality of the rubber used is specified.

Rubber extractive in intravenous injections has been suspected for pyrogenic activity, but Thompson[10] exonerates it in this respect. Only one unspecified type of rubber was investigated.

In 1941[11] I pointed out that certain types of rubber caps could react with sodium metabisulphite and reduce its protective antioxidant activity. Whittet[12] suggested that caps to be used for closing containers for injections preserved with sodium metabisulphaite should be soaked in metabisulphite solution (0·2 per cent. or more). West and Whittet[13] investigating the stability of solutions of adrenaline salts when packed in vaccine bottles stated that it was essential to use caps so treated, otherwise the solutions tended to darken in colour and lose activity. This precaution has now been adopted in the British Pharmacopœia.

We have very little reported data on the inactivation of medicaments by rubber or rubber extractives. In this respect Cowan[14] reports that different kinds of rubber had different effects on penicillin solutions, some samples inactivating a considerable proportion of the antibiotic, whilst others had no observable effect. Huelsebusch *et al.*[15] report on the stability of solutions of penicillin and streptomycin when stored in rubber tubing and assayed after 6 hours and 24 hours. There was no change in the streptomycin solution. Natural crepe rubber had no effect on penicillin solutions but other types of rubber varied from no action to an adverse action.

In the field of tissue culture and in bacteriology it has long been recognised that rubber can contribute toxic substances and invalidate experimental results. Thus Parker *et al.*[16] report toxic effects of a number of different types of rubber stoppers on animal cells in tissue cultures. Pure gum-rubber stoppers and silicone covered stoppers were much less toxic. It has been reported that the presence of tetramethylthiuramdisulphide added as an accelerator made the rubber very bactericidal and upset bacterial counts in milk. The monosulphide did not. Nikethamide has been reported as reacting with rubber and for this reason the British Pharmacopœia specifies that it shall be packed in ampoules. Conversely, this reaction has been denied. This variation in action can, I understand, be possible owing to variation in the rubber-mix.

(*c*) *The Absorption of Substances by Rubber.*

That rubber will absorb or dissolve substances is well-known to the rubber technologist and in textbooks on rubber, many examples are quoted. Much work has been done on the swelling and solution of rubber. Thus Lee[17] quoted many such substances and records their action. In this list, a few such as terpineol are of pharmaceutical interest The others are probably only of academic interest, it is noteworthy that not one of them is phenolic. We, however, would be very interested in data concerning the action of phenols on rubber, for it has a pharmaceutical aspect. We know now that phenol, chlorocresol and probably other similar water- or soap-soluble phenols can be extracted from aqueous solutions by rubber, such as rubber caps. Many cases are reported. McGuire and Falk[18] showed that 0·5 per cent. of phenol was reduced to 0·3 per cent. after 237 days at 37° C. while controls with glass stoppers showed no diminution. The rate of solution is, however, much more rapid than that. Berry has shown that in certain conditions rubber caps would reduce the strength of 0·1 per cent. chlorocresol by 75 per cent. Solutions of insulin originally protected by 0·5 per cent. of phenol have been shown to be unprotected after 12 months' storage. The amount and rate of solution of phenols in a given rubber is, I presume, amongst other factors, proportional to the area of rubber exposed, time of exposure and the temperature. A saturation point must be reached.

One presumes that ultimately an equilibrium is set up between the phenol in the rubber and in the aqueous or oily solution and that it is conceivable that if the rubber has reached saturation in respect of a strong phenol solution and is then brought into contact with water or a weaker solution, some phenol may pass back from the rubber to the water. It is possible to boil the phenol out of the rubber.

It is, of course, a serious matter if the rubber cap of a multiple-dose container should extract the protecting bacteriostatic and for this reason the Pharmacopœia specifies that caps are boiled in several changes of distilled water and then either boiled under a reflux condenser for 30 minutes, or stored for not less than 48 hours in a solution containing the same bacteriostatic in the same concentration, or preferably in twice the concentration, used in preparing the injection. Not being quite sure of itself, it adds the further caution:—On prolonged storage rubber so heated is liable to continue to absorb bacteriostatic from the injection.

(*d*) *Rubber and Disinfectants.*

Because of the reaction between phenols and rubber, I tested the reaction of several disinfectants upon it. After immersing rubber bands in the various test liquids for 7 days the degree of swelling and the alteration in extensibility and in tensile strength was noted. The results are recorded in Table I.

The bands were also tested at various periods up to one year but no other changes were detected even after 12 months. Some of the disinfectants seemed to preserve the rubber for quite contrary to what I had expected, iodine showed little effect on tensile strength even after 12

months' immersion. Similar results were obtained later by using strips cut from surgical rubber gloves. The following different reactions could be noted. The rubber might show:—

(*a*) Little change in any measurement (formalin, solution and tincture of iodine or Dakin's solution).

(*b*) An increase in extension without applying force (swelling) with an increase in maximum extension and with no appreciable loss of tensile strength (lysol, cresol, liquified phenol).

(*c*) A marked increase in extension without applying force, and a great loss of tensile strength (terpineol, eucalyptus and ti-tree oils, solution of chloroxylenol. Jeyes fluid (undiluted)).

(*d*) Complete solution of the rubber (phellandrene).

Thus in the case of terpineol or a preparation containing it (solution of chloroxylenol) the rubber swelled very considerably and in that condition it lost much of its tensile strength and became "cheesy" in texture. (It

TABLE I

EFFECT OF CERTAIN SUBSTANCES ON RUBBER BANDS AT ROOM TEMPERATURE

	Length	Maximum extension	
Control rubber bands	6·4 cm.	× 8·0 times	
	After immersion for 7 days		
	Length (swelling)	Maximum extension	Tensile strength
Distilled water	6·5 cm.	× 8·0 times	No alteration
Formalin	6·8	× 8·2 "	"
Potassium laurate soap solution	6·5	× 8·1 "	"
Dakin's solution	6·5	× 8·1 "	"
Chloramine solution	6·5	× 8·1 "	"
Cetrimide 1/1000	6·5	× 8·3 "	"
Teepol solution	6·5	× 8·6 "	"
Weak solution of iodine	6·8	× 8·3 "	"
Liquified phenol	6·9 cm.	× 8·6 "	"
Cresol	7·5	× 9·4 "	"
Lysol	6·9	× 8·8 "	"
Solution of chloroxylenol	7·3	× 9·4 "	"
" " " 1/10	7·0	× 8·8 "	"
Dettol	7·3	× 9·4 "	"
Izal (undiluted)	7·2	× 8·9 "	"
Jeyes Fluid 1/10	7·5	× 9·2 "	"
" 1/20	7·2	× 8·8 "	"
" 1/40	6·9	× 8·7 "	"
Jeyes Fluid (undiluted)	10·1 cm.	—	Almost complete loss
*cyclo*Hexanol	7·2	—	"
Methyl*cyclo*hexanol	8·2	—	"
Terpineol	10·5	—	"
Eucalyptus oil	10·5	—	"
Ti-tree oil	9·4	—	"
Pine oil	9·2	—	"
Phellandrene	Dissolved	—	—

would appear wrong therefore to use solution of chloroxylenol on rubber gloves.) If, however, the rubber be then soaked in ethanol, the terpineol dissolves out, the rubber contracts to its original length and regains its original tensile strength. In a like manner phenol or cresol can be boiled out of the rubber and the band returns to its original length.

The action of iodine and hypochlorites is interesting, for apparently there is a chemical reaction at the surface of the rubber which does not

penetrate inside. It leaves a glossy film on the surface, which improves the appearance, and, I understand, increases its resistance to the absorption of water. It certainly improves rubber caps to immerse them in hypochlorite solution for about 1 hour and then boil in water. The surface is not liable to hold particles, and greasiness is removed.

The action of cresol and lysol was interesting as the rubber absorbed a considerable amount of the phenol with no obvious signs of deterioration in character. It is obvious that the surface of rubber so treated must be highly bactericidal (when moist). Indeed, this can easily be shown if a segment of such rubber be washed in sterile water and plated out in a bacterial seeded agar. On incubation an appreciable clearance zone will show. This raises the point as to whether surgical rubber gloves should ever be immersed in a solution of lysol. I remember during the war being invited to attend a meeting of surgeons to discuss the problem of the shortage of surgical rubber gloves and the unpalatable alternative of operating with bare hands. Methods of sterilisation by immersion of the gloves in solutions of lysol were discussed and quickly discarded. The opinion was freely expressed that rubber gloves after immersion in a solution of lysol became unsuitable in that on touching tissues they were liable to cause adhesions, presumably because of the high concentration of cresol at the surface. It is only fair to say that Colebrook in his treatise on the Disinfection of Skin in 1941[19] recommended lysol 2 per cent. for use on rubber gloves after placing them on the hands and stated that iodine 2 per cent. in aqueous solution with 2 per cent. of sodium iodide was the most rapidly effective but it is also somewhat damaging to the rubber. Craig *et al.*[20] suggest similar methods including the use of solution of chloroxylenol or biniodide of mercury 1 in 250. Wright[21] recommends treatment with 1 in 1000 perchloride of mercury. Stuart[22], however, deprecates the immersion of the gloves (not on the hands) in any antiseptic on the grounds that rubber deteriorates when so treated and the trace remaining may cause damage to the skin of the surgeon's hands. The opinions, therefore, cancel out. It is unlikely that iodine or hypochlorites will leave the rubber surface bactericidal as there would appear to be a chemical reaction between them and the rubber, and no free iodine would remain.

These attempts to sterilise rubber gloves with disinfectants are probably now of historical interest only for there is general agreement, I think, that rubber gloves should be wet-heat sterilised and that modern rubber can withstand autoclaving many times at 105° to 115° C. It has been agreed that a good detergent wash prior to wet-heat sterilisation contributes a great deal to the efficacy of the sterilising and therefore to the use of minimum heat treatment. It is also now well known that it is very unwise to subject rubber gloves to dry heat. One effect of lysol on rubber in hospital practice is, however, well known—that it is possible to get cresol "burns" from rubber bed sheeting that has been washed with a solution of lysol. Presumably this is due to the concentration of cresol on the rubber surface.

I think we ought to keep reminding ourselves that the results of any

experiments concerning rubber depend upon the material. I am conscious that the results I have reported with the rubber bands are strictly only applicable to those particular bands and type of rubber mix. Mr. Haworth stresses the point that even though the formula of a rubber mix is agreed and standard auxiliary substances are specified, the main constituent, raw rubber, varies just as much as any of our own "unorganised" drugs do. Even if that too be standardised, the result can still depend upon the operator in his control of the process; spotted and discoloured surfaces reacting badly in use may result from bad mixing, as well as from different physical characters. Careless control of a vulcanising temperature may result in a rubber with a sticky surface which in turn yields an oiliness to an aqueous solution.

Therefore, I would like to ask Mr. Haworth, knowing now some of our problems, if he can suggest how we could devise specifications for a pharmaceutical rubber with all the requisite physical characteristics and long life and yet be non-reactive with any medicament. The Pharmacopœia merely states that the rubber for rubber caps should be good quality heat-vulcanised rubber.

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DISCUSSION

MR. G. SYKES (Nottingham) said that from his experiments on bacteriostatics and rubber, phenol appeared to be the best of the regular preservatives while the worst was phenylmercuric nitrate. He asked Professor Berry whether he had any information on the quaternary compounds in that connection. It seemed that there was a short-term effect of immediate surface absorption, in which the surface area might be significant, and a long-term effect in which diffusion of the preservative took place throughout the rubber, in which case the weight ratio was probably the significant factor. It would be interesting to have Professor Berry's opinion on the adequacy of the B.P. treatment of rubber caps for sterile containers, and on the value of such treatment in terms of the period of storage. It would also be interesting to learn whether Mr. Haworth had ever experienced mould growth in rubber.

DR. H. DAVIS (London) referred to the question of the flaking of glass, and said that during the war he had experienced considerable trouble with sodium citrate solutions after autoclaving and had reached the conclusion that the flakes were silica. Empirical methods were adopted, and every batch of bottles was autoclaved containing sodium citrate solution, and those which flaked were discharged. He had found that glass autoclaved with a solution of sodium metabisulphite, did not flake as much as untreated glass. Was there any relationship between that result and Miss Dimbleby's comments on sulphur dioxide-treated glass? Blood products were controlled by the Therapeutic Substances Regulations which made the purely negative suggestion that citrated blood should be in a non-flaking container. It would be of advantage if a glass were available which was guaranteed not to flake with contents of that type so that a suitable container could be specified.

With regard to the absorption of phenolic disinfectants on the surface of rubberised sheets, etc., it should be strongly emphasised that there was a risk of producing dermatitis and phenol burns as a result of soaking such sheets in weak solutions of those disinfectants.

MR. T. D. WHITTET (London) said it was interesting to note that it was customary to put some sodium sulphite in pale crêpe rubber, and he wondered whether that persisted, because it might explain some results he had obtained. He had found that metabisulphite appeared to have only a surface action. Rubber caps soaked in metabisulphite were bleached almost white, but only on the surface.

MR. COOPER (Bristol) said that on storage of intravenous solutions in M.R.C. bottles with black rubber wads, a fine film of powder was produced after six months. It appeared to be protein material. He asked Mr. Haworth whether he had any views on the deproteinisation of rubber. He had treated the wads by washing with alkali, then with acid and finally boiling with distilled water. The solution obtained by boiling 100 caps in 2 l. of water was extracted with chloroform and an

oily residue was left amounting to about 14 mg. He wondered whether this oil might be carcinogenic.

MR. W. F. HARTE (Nottingham) asked whether any of the authors had experience of silicone-treated rubber to prevent soluble matter from the rubber entering the solution, or *vice versa*.

MISS V. W. BURRELL (Harrow) referred to the increased surface stability of sulphur-treated glass containers. With regard to the absorption of antiseptics by pure latex rubber bands, tests using respectively 1 per cent. phenol, 0·5 per cent. chlorbutol, 0·3 per cent. chlorocresol, and 0·002 per cent. phenylmercuric nitrate, showed that after storage at 37° C. for 1 to 3 months there was a loss in concentration of the antiseptics; phenol was still present in the highest amount, while phenylmercuric nitrate was not detectable. On using a concentrated solution of phenylmercuric nitrate in order to effect saturation, the rubber became unsightly with black specks.

PROFESSOR H. BRINDLE (Manchester) asked for information on silicone coating of the interior surface of glass bottles. From Professor Berry's preliminary experiments it would appear that there were advantages in a silicone coating. One advantage which was not mentioned was that it enabled practically 100 per cent. recovery of liquid from a bottle or ampoule. That would appear to be a considerable economic advantage where expensive injections were being used.

MR. H. S. GRAINGER (London) said he understood that many of the syringes used in hospitals were of soft soda glass, and it was well known that they deteriorated rapidly as a result of repeated boiling. It had been observed that when detergents of the sulphestol type were employed for washing syringes there was a great tendency for them to discolour when dried at 150° C. It had been suggested that the use of that type of detergent caused more rapid deterioration of the glass surface. He was using syringes of borosilicate glass of the interchangeable piston type, and so far that type had not shown the same tendency towards deterioration as soft glass.

MR. J. H. OAKLEY (London) asked Miss Dimbleby whether glass bottles normally used for pharmaceutical purposes should be allowed to weather for a period and, if so, what was a reasonable period so that when washing took place prior to use, the maximum amount of alkali was removed. Magnesium hydroxide reacted with a manganese-containing glass resulting in the formation of a layer of manganese dioxide on the surface. More attention should be paid to the bonding materials used in "compo" corks to render them less liable to mould growth, and with cut corks a more efficient means than wax was required for surface treatment. There was also a need for an economical but more durable lining for drums used for the transport of galenicals.

MR. C. E. TURNER (Stoke-on-Trent) said that in his experience dropper bottles containing solution of atropine methonitrate, although apparently perfectly sealed, showed evaporation of the product after a month. He asked whether the rubber cap was a suitable closure for that type of

preparation, and whether the solution had an effect on the rubber cap which caused evaporation.

MR. BROOKS (Nottingham) said he had found that for the majority of bottles the most suitable type of rim was a convex surface which pressed on to the liner of the cap. Mould marks on the top of a bottle causing tearing of the liners was a problem, but it was now possible to obtain bottles which had them removed. Where aluminium was employed for capping, a special hard tempered material should be used. A type of well for the liner in plastic caps could be made by cutting the thread short before it reached the top of the cap. Resin-bonded "compo" was superior to cork liners in reducing mould growth. Blackol and tinfoil were useful liner materials because of their inert nature but it was difficult to obtain a tight seal. Polythene liners were also somewhat difficult to seal, but they were useful for reactive materials and for low boiling point liquids.

DR. R. RUYSSEN (Belgium) referring to the release of material from rubber caps said there was some danger of contaminating solutions with zinc or other heavy metals. Traces of copper or zinc would catalyse the oxidation of organic substances in solution. He suggested four tests to be applied to rubber caps. There should be no change in concentration of medicinal solutions. There should be no change of the *p*H. Heavy metal contamination should not occur, and lastly fillers should not be released as shown by a turbidity test. For the pretreatment of rubber caps before sterilisation alkali should not be used but sodium phosphate solution having a *p*H of about 8. He asked Miss Dimbleby the action of sodium phosphate on glass, because pretreatment of caps would be carried out in glass containers.

DR. R. M. SAVAGE (Barnet) suggested that manufacturers could not always apply the knowledge they had in meeting consumers' requirements because the cost would be too high in relation to that of a mass produced article of inferior quality.

MR. ROSS (Liverpool) said that natural rubber, being of botanical origin, was inherently variable, and a more fruitful source of investigation for the ideal closure would be among the synthetic rubbers. The efficiency of screw caps depended almost entirely on the suitability of the wad. Resin-bonded cork had still to prove itself better than gum-bonded cork for preventing mould growth. He had seen polyethylene bonded composition corks, but they did not seem to be commercially available. Material used for stuffing tablet bottles could contain a surprising amount of moisture which might have a deleterious effect. In his experience lead-bound metal containers were the only satisfactory containers for ether.

MR. V. REED (London) asked whether there was anything in the composition of glass measures which would make some more liable to crack than others. He also asked whether differences in colour of rubber caps were related to the absorption of phenolic preservatives.

MR. MELLOCK (Chessington) asked for information with respect to containers for volatile liquids such as ether which would stand up to high altitudes.

MR. P. J. FOWLER (Bristol) said that he had experience of a syringe service and a sulphonated detergent was available for use in washing which did not cause discoloration of the syringes.

MR. A. J. DOUGLAS (Horsham) referred to Mr. Stephenson's humidity test for the efficiency of closures and to his statement that paper-filled urea-formaldehyde caps absorbed up to 4 per cent. of their weight of water and asked whether he used any controls in such cases to rule out a small source of error.

He found that tinted white flint glass bottles were more liable to flake than the pure white bottles.

DR. G. E. FOSTER (Dartford) said that if some specification for rubber were devised the rubber would have to be tested. That would necessitate obtaining a representative sample of rubber, which was more easily said than done.

MISS I. R. HARRIS (Bromley) said she had found that by storing sterile sodium citrate solutions in amber glass bottles there had been no problem due to flaking.

MR. D. STEPHENSON, in reply, said that he had no answer to the problem of coating corks with some moisture-impervious substance. The treatment of corks with a solution of a plastic was not an economical proposition. He had searched for a plastic material with a sharp melting-point; polythene had a long melting range. In his experience, whilst the majority of bottles had a domed rim, a flat rim gave a better seal. With the correct tightness on the wad and a flat rim there was a wide distance between the material and the outside atmosphere giving the likelihood of a good closure. The lack of a recess for wads in plastic caps was due to the method of moulding plastics. As to composition corks, polythene bonded cork was available and would probably meet many of the criticisms. Some forms of polyvinyl chloride might provide suitable substitutes for rubber for injection products.

Cellulose fibre used for stuffing tablet bottles needed to be dried as it could contain 12 to 15 per cent. of moisture. With containers for high altitudes as much air as possible should be excluded. Flexible containers were advisable.

MISS V. DIMBLEBY, in reply said that in washing with water or dilute acids the reagent extracted some of the sodium ions in the glass surface leaving a thin layer with more silica and less alkali than underneath. The resulting increase in resistance might not be very evident on long storage or with alkalis. Washing with detergents, especially if alkaline might attack the silica skeleton of the glass, forming hydrated silica to some extent and leading to adsorption of some colouring material.

Weathering needed careful control. The lime might be extracted, and a silica layer would be left which had not the same reflecting or transmission qualities as the glass itself so that it appeared as a white deposit

on the surface. In some experiments a number of ordinary 4 oz. medicine bottles after weathering for 9 months gave a better response in the 5 hour boiling test, with water than they did when new, but they flaked more readily. When the weathered layer attained a certain thickness, it ceased to have the same expansion as the glass behind and no longer adhered.

Sodium phosphate solutions always caused flaking in a short time. There was a similar action with sodium citrate, but in association with other workers at Sheffield interested in storing blood she had found that there was a big difference in the behaviour of different types of glass towards sodium citrate solutions on autoclaving. This work would be published in the near future.

Silicone coatings were very useful if it was essential to recover the last drop of any expensive liquid. On repeated autoclaving, however, the coatings would gradually come away from the glass. The coating was on the glass; it was not a silica layer made from the glass structure itself. Unless the glass was thoroughly clean to start with so that the coating contained no pinholes and was impermeable to moisture, flaking might occur. Sulphuring of glass surfaces undoubtedly rendered them more resistant to the action of water for a period, but work on the extraction of arsenic had shown that the treatment was no use for long storage, especially of alkaline solutions.

All methods of testing glass were empirical. Glass had no solubility; the problems arose from the decomposition of the glass surface. The method of testing should be that which simulated as nearly as possible the service conditions, but a good safety margin should be allowed by increasing the temperature, the surface area of the glass exposed to attack, or the strength of the reagent.

MR. J. HAWORTH, in reply, said that natural rubber was treated either by smoking to absorb phenols or with sodium sulphite, to prevent surface mould growth during storage in the tropics. Persistence of sodium sulphite in pale crêpe rubber was probable. He was not sure whether the reaction between metabisulphite and rubber was a purely surface action. In the first few hours of contact between metabisulphite and pieces of rubber there was a fairly rapid action, and then no further change seemed to occur, but the thickness of the rubber and the rate of penetration, associated with the degree of vulcanisation, were involved. Changes of colour of the rubber surface could be due to actual changes in colour or to changes in the refractive index as a result of water absorption; very often these effects were confused.

Deproteinised rubber was more costly. He was interested in the report on the extraction of an oily residue from rubber which, it was suggested, might be carcinogenic. Many of the softeners used were of coal tar or petroleum origin and might be carcinogenic. Carbon black, which was a very popular filler, often contained a proportion of oily material which could be extracted by solvents, and which had recently been shown to be carcinogenic.

Silicones in his experience all gave trouble. Differences in the absorption of phenols were connected with variations in the degree of vulcanisation

and with the extent of cross linkage. The colour of the rubber did not affect the absorptive properties. The best hope of controlling the evaporation of volatile solvents seemed to lie in the different types of synthetic rubber.

On the question of choosing a representative sample, he had pointed out that one of the difficulties in testing rubber was the type of test. In testing simple properties such as tension strength it was necessary to use special machinery in order to obtain reliable results and to treat the results on different samples on a statistical basis.

On the question of economics, only 0·45 per cent. of the natural rubber imported in 1952 went into the manufacture of surgical rubbers, so the manufacturers had very little say in what the plantation industry provided.

PROFESSOR H. BERRY, in reply, said that Mr. Sykes would probably find that if he changed his rubber he would obtain large differences in the rate of absorption of bacteriostatics. The B.P. played for safety. Rubber could be made highly fungicidal. If the silicone treatment were adopted it would be necessary to get used to the greasy appearance, which might be difficult to explain to a lay person. He could not give any opinion on the question about solution of atropine methonitrate.