potency index of the unknown. Divide the potency index of the reference standard phenolphthalein by that of the unknown to determine their relative potency.

Results not falling within the range of error previously determined for the reference standard can only be considered indicative of the unknown potency. Adjustments of the unknown dosage level are then necessary and the assay re-run at this adjusted level.

DISCUSSION.

Subsequent reports will be presented covering the assays of unknown samples of phenolphthalein and other laxative substances.

We believe that the rhesus monkey is as near the ideal test animal for laxatives as is possible to find. This is borne out by the fact that the mg. per Kg. doses required by the monkey when calculated on the basis of the human are practically identical.

CONCLUSIONS.

1. A procedure for the bioassay of phenolphthalein using the rhesus monkey has been developed and found satisfactory.
2. Individual rhesus monkeys require different threshold doses of phenolphthalein.
3. This bioassay method might be found applicable to all other laxatives.

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PHARMACEUTICAL USES OF THE GLYCOLS AND THEIR DERIVATIVES.*

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The use of the glycols and their derivatives in Pharmacy is of comparatively recent origin but is increasing rapidly or was, until the occurrence of the "Elixir of Sulfanilamide" tragedies, a little more than a year ago. While it is a fact that ethylene glycol was prepared by Wurtz (1) in 1859 and that its possibilities as a substitute for glycerol were called attention to by a number of investigators over the next fifty or sixty years, little, if any, consideration was given to it or to the glycols prepared later (2) until after the World War. Prior to this time, alcohol was the solvent generally used by pharmaceutical manufacturers. It was cheap, there were no burdensome restrictions on its use and it was deemed to be as satis-

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factory as could be expected in other ways. With the passage of the Federal laws governing the manufacture, sale and use of alcohol which followed our entry into the War, these conditions changed. A heavy tax was placed upon alcohol and the restrictions thrown about its use were made more exacting, the first of which increased the initial cost and the second of which increased the cost of handling. The increase in production costs to the manufacturer as a result of these changes coupled with a decrease in price of the glycols as a result of the development of more economical methods of manufacture and of production on a large scale paved the way for the more general use in Pharmacy of the glycols and their derivatives.

In view of the fact that the glycols and their derivatives possess certain advantages over alcohol, *i. e.*, most of them are excellent general solvents possessing to a degree the combined solvent properties of both, alcohol and water, boil over a fairly wide range of temperatures, et cetera, it is astonishing that an economic stimulus was required to drive manufacturers to their use. It may be assumed, however, that the apparent inertia on the part of the pharmaceutical manufacturers in particular was not due so much to their unwillingness to avail themselves of the advantages offered by these new solvents as to fear of the injury which might be done to the products manufactured or to the users thereof through the use of untried materials. That this fear was well founded is borne out by the fatalities which resulted from the use of the elixir heretofore mentioned and by the more recent work done on the pharmacology and toxicology of these compounds (3).

Just when the glycols and their derivatives were first used in Pharmacy, I have not been able to discover, but it can be stated that their use in pharmaceutical manufacturing was antedated by their use as solvents in the lacquer industry for which some of the glycols and their alkyl ethers were being produced on a commercial scale twelve or more years ago (4). Further, that the first use of glycols in articles intended for human consumption was as a vehicle in flavoring essences and that this also occurred twelve or more years ago (5). Ten years ago, Lawrie (6) wrote ethylene glycol is now being produced synthetically in large quantities but there is not a wide market for it and, in 1932, Seidenfeld and Hanzlik (7) reported that, although propylene glycol is obtainable commercially, it has commanded little or no interest in Chemistry and Medicine. From the foregoing, it seems safe to assume that the use of the glycols and their derivatives in Pharmacy does not go back farther than ten years. That there has been a marked increase in the extent of their use in this field in the last five years is indicated by the increasing frequency with which they are mentioned in the literature covering this period.

The glycols which have been suggested as suitable for use in Pharmacy and those which are actually being used at the present are the lower members of the series, those containing less than six carbon atoms, and the derivatives used or suggested for use are certain ethers, alkyl esters and amino derivatives of these lower members. Taken together, they make quite a formidable list as is shown in the following table. The higher members of the series have evidently not received attention because most of them are solids at ordinary temperatures and the boiling points are beyond the desirable range.

The properties of the compounds listed which make them especially suitable for pharmaceutical use may be summarized briefly as follows: Most of them are

TABLE I.—GLYCOLS AND DERIVATIVES USED OR SUGGESTED FOR USE.

W = water. s. s. = slightly soluble.
A = alcohol. v. s. = very soluble.
E = ether. ins. = insoluble.
∞ = soluble in all proportions.

Name of Compound.	Chemical Formula.	Physical State. (ord. temp.)	Boiling Point. (approx.)	Solubility.
Ethylene glycol	$HOCH_2.CH_2OH$	Col. liq	197.2° C.	∞ W, ∞ A, 7.89 E
Ethylene glycol monoacetate	$CH_3COOCH_2.CH_2OH$	Col. liq.	182° C.	∞ W, ∞ A, E
Ethylene glycol monomethyl ether	$CH_3OCH_2.CH_2OH$	Col. liq.	124 °C.	∞ W, v. s. A, s. E
Ethylene glycol monoethyl ether	$C_2H_5OCH_2.CH_2OH$	Col. liq.	135.1° C.	∞ W, ∞ A, ∞E
Ethylene glycol monoethyl ether acetate	$CH_3COOCH_2.CH_2OC_2H_5$	Col. liq.	156.2° C.	22W, ∞ A, ∞ E
Ethylene glycol diethyl ether	$C_2H_5OCH_2.CH_2OC_2H_5$	Col. liq.	123° C.	
Ethylene glycol monobutyl ether	$C_4H_9OCH_2.CH_2OH$	Col. liq.	170.6° C.	∞ W, ∞ A, ∞ E
Ethylene glycol monophenyl ether	$C_6H_5OCH_2.CH_2OH$	Liquid	165° C.	
Diethylene glycol	$HOCH_2CH_2.O.CH_2CH_2OH$	Col. liq.	244.5° C.	s. W., s. A., s. E
Diethylene glycol dilaurate	$(C_{11}H_{23}COOC_2H_4)_2O$	Yel. liq.	250° C.	Disp. W, ∞ A, ∞ E
Diethylene glycol dioleate	$(C_{17}H_{33}COOC_2H_4)_2O$	Oily liq.	.....	Disp. W, ∞ A, ∞ E
Diethylene glycol distearate	$(C_{17}H_{35}COOC_2H_4)_2O$	White solid	.....	Disp. W, ins. A., ins. E
Diethylene glycol monoethyl ether	$CH_3OCH_2CH_2OCH_2.CH_2OH$	Col. liq.	193.2° C.	∞ W, v. s. A, s. E
Diethylene glycol monobutyl ether	$C_4H_9OCH_2CH_2OCH_2.CH_2OH$	Col. liq.	231.2° C.	∞ W, v. s. A, v. s. E
Trimethylene glycol	$HOCH_2CH_2CH_2OH$	Visc. liq.	214° C.	∞ W, ∞A, v. s. E
Trimethylene glycol methylene ether	$OCH_2OCH_2CH_2CH_2$	Col. liq.	105 °C.	∞ W, ∞ A, ∞ E
Triethylene glycol	$(CH_2OCH_2CH_2OH)_2$	Col. liq.	280°–290° C.	∞ W, ∞ A, s.s. E
Triethylene glycol monoethyl ether	$C_2H_5OCH_2CH_2OCH_2.CH_2OH$	Col. liq.	197° C.	∞ W, ∞ A
Ethanolamine	$HOCH_2.CH_2NH_2$	Col. liq.	172.2° C.	∞ W, ∞ A, 0.72 E
Triethanolamine	$N(CH_2CH_2OH)_3$	Visc. liq.	277° C.	∞ W, ∞ A, s. s. E
Propylene glycol	$CH_3OH.CHOHCH_3$	Col. liq.	189° C.	∞W, ∞ A, s. E
α-Butylene glycol	$CH_3CH_2CH(OH).CH_2OH$	Liquid	192 °C.	s. s. W, ∞ A
Pseudobutylene glycol	$CH_3CH(OH)CH(OH)CH_3$	Liquid	184° C.	∞ W, ∞A, ∞ E
Isobutylene glycol	$(CH_3)_2C(OH)CH_2OH$	Liquid	177° C.	s. W
β-Amylene glycol	$CH_3CH_2CH(OH)CH(OH)CH_3$	Liquid	187° C.	s. W., s. A
α-Isoamylene glycol	$(CH_3)_2CHCH(OH)CH_2OH$	Liquid	206° C.	s. A., s. E
β-Isoamylene glycol	$(CH_3)_2C(OH)CH(OH)CH_3$	Thick liq.	177° C.	∞ W, ∞A, ∞E

liquid at ordinary temperature; they are almost odorless or the odor is not objectionable; the taste is not objectionable, being sweetish as a rule; they boil at temperatures ranging from about 105° C. to 290° C.; most of them possess to a degree the combined solvent properties of alcohol and water; they can be dehydrated by heating; they inhibit the growth of microörganisms (8) when diluted and may, therefore, be used as preservatives; some of them, the esters of the higher fatty acids and the ethanolamines, are good emulsifying agents.

The above enumerated properties suggest as possible pharmaceutical uses for these compounds their utilization as solvents for the preparation of simple solutions and as menstrua for the extraction of drugs, as vehicles for carrying medicaments in solution or in suspension, as emulsifying agents for the preparation of creams and ointment bases and as preservatives for medicinal preparations. That these possibilities are steadily developing into actualities is revealed by the following information obtained from the available literature or from other sources.

Etylene Glycol.—As early as 1917, Bachem (9) stated that ethylene glycol was worthy of consideration as a substitute for alcohol in preparations containing iodine whether intended for

external or internal use. He also reported that it "mixes" readily with phenol, mercuric chloride, tannin, potassium iodide, tincture of iodine, lactic acid, salicylic acid, boric acid, menthol, thiogenol, tumenol, ichthyol and soap but not with fats and ethereal oils. Further, that it has been used successfully in mixture with ointments, with gelatin suppository bases and in the preparation of enemas, surgical dressings, cosmetics and preparations intended for local application in the nose, vagina and anal fissures.

In 1924, Fuller (10) called the attention of American manufacturers to the possibilities of using ethylene glycol as a substitute for alcohol in the manufacture of liquid medicinal preparations and reported that it possessed bacteriostatic properties.

In 1931, Hanzlik and co-workers (11), as a result of investigations on ethylene glycol as a substitute for glycerol, reached the conclusion that the former is an excellent general solvent; dissolves salts readily, many heavy metal salts, barbital, alkaloids, iodine, etc., and that it makes collodion pliable.

John Rae (12), in 1933, reported the results of experiments on the extraction of vegetable coloring matters with ethylene glycol. The results showed the glycol to be superior to alcohol in the extraction of the coloring matter of cudbear, red saunders, red rose petals, madder, saffron, Brazil wood, henna and cochineal.

In the February 13, 1932, number of the *Journal of the American Medical Association*, there appeared the advertisement of a well-known pharmaceutical manufacturer for a preparation to be used in the treatment of syphilis. This advertisement carried the statement that the preparation was a solution of sodium iodobismuthite in ethylene glycol (13). It is reported that propylene glycol is now used in place of ethylene glycol. A solution of sodium bismuthate in propylene glycol has been suggested as a more satisfactory preparation by Hanzlik and coworkers (14).

In 1936, Dr. Hinton (15) reported successful results in the treatment of inflammatory processes with a paste composed of magnesium sulfate and ethylene glycol.

A manufacturer of glycols (16) has supplied the information that anhydrous ethylene glycol is used to prepare sterile solutions of the barbiturates and that it is a suitable solvent for benzocaine in conjunction with acetylsalicylic acid.

Ethylene Glycol Monoethyl Ether.—As far back as 1927 (17), attention was called to the possible use of monoethyl ether of ethylene glycol as menstruum for the preparation of galenicals and for the extraction of the pungent principles of drugs and spices. Numerous references to its use in the preparation of cosmetics will be found in "Cosmetic Dermatology" by Goodman.

Ethylene Glycol Monoacetate.—This glycol ester has been suggested for use in the separation of medicinal paraffin from the other paraffines and is stated to be a good solvent for the essential oils (18), but there is no evidence that it is now being used for either of these purposes.

Diethylene Glycol.—Although frequently referred to in the literature as a good solvent for medicinals, there is no evidence to show that it is in actual use for this purpose at the present time.

Diethylene Glycol Monoethyl Ether.—This compound has been suggested as a suitable solvent for benzocaine in conjunction with acetylsalicylic acid (19). Stable solutions which do not require alcohol are said to be thus obtained.

Diethylene Glycol Dilaurate, Dioleate and Distearate.—Diethylene glycol oleate is used for making solutions of oils and for the preparation of emulsions of both, the oil in water and water in oil types (20).

The dilaurate is used as a solvent for oil-soluble dyes where the latter are to be incorporated in an aqueous mixture, to replace sulfonated oils in pharmaceuticals and cosmetics and for the preparation of emulsions. A special grade (neutral) with a p_H of 6.9 is prepared for the pharmaceutical and cosmetic trades (20).

The distearate is reported to be an excellent emulsifying agent for fatty oils, hydrocarbons and waxes. It disperses in hot water with the production of viscous fluids or creams, hence it may be used to replace the vegetable gums, tragacanth, karaya and quince, in certain types of preparations. It is used in the cosmetic industry for the preparation of lotions and creams. In pharmaceutical manufacturing, it is also used as a lubricant or to provide a protective coating for hydroscopic powders, crystals, tablets, troches, etc. It is used in nebulæ and ointment bases to make possible the removal of greasy stains by washing with water (20).

Triethanolamine.—Within the last five or six years, triethanolamine, which may be looked upon as an amino derivative of three molecules of ethylene glycol, has developed from a laboratory curiosity into a commercial product of many and varied applications. In certain respects, it exhibits the combined properties of glycerol and ammonia. It is used for the preparation of cosmetic emulsions (21) and in dermatologic therapy (22). In Pharmacy, it is used in the form of the stearate for the preparation of ointment bases. A formula for a paraffin oil emulsion intended for internal use in which triethanolamine stearate is the emulsifying agent selected has been elaborated by Norstroem (23).

Trimethylene Glycol Methylene Ether.—Jordan (24) states that this glycol ether is used for the extraction of ethereal oils and is a good solvent for many substances used in Pharmacy.

Triethylene Glycol.—While this glycol has been suggested as a solvent which might have some pharmaceutical application, there is no evidence of its use at the present time (25).

Propylene Glycol.—It was suggested by Hanzlik and co-workers (26) in 1931 that propylene glycol offered possibilities as a solvent or vehicle for medicinal preparations.

In 1935, Brown (27) summarized the conclusions which he reached after a fairly comprehensive study of the suitability of this glycol as a solvent for pharmaceutical use as follows:

1. "In assaying propylene glycol galenicals, involving the use of ether or chloroform for extraction, the galenical should be diluted with at least one-fifth of its volume of water.
2. Solutions of certain alkaloids in propylene glycol can be freely diluted with water without precipitation.
3. Propylene glycol tends to mask the reactions of certain alkaloidal reagents, notably picric acid and tannic acid.
4. Phenolphthalein can be dispensed in solution in therapeutic doses.
5. The halogen salts of sodium and potassium are very soluble in propylene glycol.
6. Dyes are readily soluble. The glycol would therefore be a suitable preservative.
7. Propylene glycol would make a suitable preservative for syrups.
8. It is a solvent for most volatile oils.
9. It may be a suitable menstruum for tinctures (especially senega) owing to its non-volatility, its solvent powers, miscibility with water and alcohol and its preservative action.
10. Propylene glycol considerably retards the volatilization of ethyl nitrite and may conveniently replace alcohol in Sweet Spirit of Nitre."

Ray (28), in a report made in 1935 of some work done on this glycol stated that it dissolves the active constituents of aloes and the tannins in catechu. In a subsequent paper (29), he reported that it was an excellent solvent for vegetable coloring matters and could be used to replace ethylene glycol for this purpose.

Propylene glycol has been used as a solvent for some of the vitamins. An advertisement, which appeared in one of the pharmaceutical journals (30) in 1936, carried the statement that the preparation advertised was a solution of pure crystalline vitamin D in propylene glycol. Data on the treatment of rickets in children with this preparation were reported by Albright, *et al.* (31), in 1937.

Jaros (32), in 1936, reported on the use of propylene glycol as a solvent for benzyl alcohol and diothane in a topical anesthetic for tonsillextirpy.

The successful use of a solution of paraldehyde in propylene glycol as an anesthetic for the relief of pain in labor was reported by Douglas and Peyton (33) in 1937.

Propylene glycol is reported to be used to prepare anhydrous solutions of the barbiturates of sufficient stability to permit of sterilization (34).

Propylene Glycol Stearate.—The stearate of propylene glycol has been found to make an excellent base for suppositories (35). It melts at body temperature, is not irritating and does not leave grease spots.

While it is true that the available literature makes mention of the foregoing, only, as being used for pharmaceutical purposes, it is possible that other sources of

information might disclose additional uses to which these compounds are being put in this field and that some of the other seventeen glycols and glycol derivatives listed in the table are also being used.

At the present time, too little is known about the physiological action of these compounds and of their practical value to predict the nature or extent of their future use in pharmacy. It seems safe to assume however, that the use of those which are found to be non-toxic in the quantities usually used will increase while those which are found to be harmful will be discarded.

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