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Phenolsulfonphthalein inhalation studies of the efficiency of a glycerin-propyle NE glycol mixture as a detergent in aerosols

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PHENOLSULFONPHTHALEIN INHALATION STUDIES OF THE EFFICIENCY OF A GLYCERIN-PROPYLENE GLYCOL MIXTURE AS A DETERGENT IN AEROSOLS

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The use of aerosol therapy in medicine is not new. The fumes of incense to drive away evil spirits, the burning of sulphur candles to disinfect the air, the spraying of operating rooms with germicidal materials have all had evolutionary significance in our thinking. Steam inhalation and the inhalation of the smoke of asthma powder are early and still useful examples of aerosol therapy of the lungs. Indeed, when the physician recommended that his patients go to the beach for the benefits of salt air, he was unwittingly suggesting the therapeutic use of the tiny salt particles in the air produced by the atomization forces of the breakers. Many pharmacologically active drugs have been employed. In the last two decades, perhaps most of the emphasis has been placed upon the use of antibiotics such as penicillin, sulfonamides, epinephrine, streptomycin, bacitracin, neomycin, and more recently, hydrogen peroxide and mucolytic enzyme aerosols in the topical therapy of the lungs and bronchi.(1,2,3,4,5)

At the present time, inhalational or aerosol therapy is a valuable technique employed to combat reversible respiratory obstruction secondary to pulmonary inflammation. It combines the use of mist therapy and air-oxygen-helium mixtures directed to the site of obstruction in the air passages. It is a form of treatment requiring

both intimate knowledge of the pathology of the pulmonary tree and skill in the use of the equipment necessary for adequate nebulization of medications.[6]

It is not the intent or purpose of this paper to cover all of the various aspects of aerosol therapy. It is, however, important to have a general understanding of the candidates for therapy, equipment and solutions used and the definitions of the various closely related terms. Then, more specifically, research data on one particular phase of aerosol therapy will be presented; that involving the carrier solutions used in therapy.

Aerosol therapy is indicated whenever there is evidence of retained secretions, mucosal edema, or both. Among the conditions benefiting from such therapy are serious rhino-sinusitis, acute epiglottitis, laryngeal edema, subglottic croup, laryngotracheo-bronchitis, foreign body bronchitis, bronchiolitis, acute bronchitis, chronic bronchitis, bronchiectasis, asthma, and cystic fibrosis of the pancreas. Conditions particularly responsive to this type of treatment are laryngotracheo-bronchitis, bronchiolitis, severe asthma, and the chronic suppurative lung such as that associated with cystic fibrosis. One caution is that of too rapid liquefaction of secretions without adequate drainage.

This can be overcome by proceeding more slowly and with adequate suction available.

The types of equipment used in aerosol therapy vary with the companies that manufacture them. Therefore, only the general principle will be discussed. That consists of a nebulizer type apparatus capable of holding the solution to be vaporized plus an air inlet and a baffle plate beyond which the vapor is channeled into the respiratory passages of the patient. The air source mentioned may be in the form of a compressor pump or just bottled oxygen. A point of interest in regard to the variable types of equipment is that the vapor delivered varies likewise. Thus, Abramson in a paper to the Fourth Annual Session of the American College of Allergists, March 1948, recommended that aerosol delivery should be certified by the manufacturer of the nebulizers and that claims should be supported by acceptable laboratory evidence.

Before discussing the solutions used, it is perhaps advisable to define more clearly a few terms which have different meanings to different people. Aerosols of the type under discussion are suspensions of particles in a gas, produced by air jets, explosions, condensation of a vapor, or by any other method. Atomization procedures, in contrast, usually produce aerosols or mists in larger

particles due to the fact that the equipment contains no baffle for collision with the spray droplets. The word nebulization is frequently confused with the above terms. It should, however, be restricted to atomization in which the large particles are removed by the introduction of a suitable baffle.[1] Such is the equipment used in this project and described in the preceding paragraph. Finally, the word vapor should be clarified by defining it as the gaseous form which a solid or liquid takes when heated. The particles are of molecular size and are therefore about 10,000 times smaller than the particles of therapeutic aerosols.[1]

Because the aerosol is carried by inspiration deep into the respiratory tree and deposited therein it is easy to see that the movement and deposition within the lungs depends somewhat on particle size. Also, it is obvious that the efficacy of aerosol therapy depends on the ability of the particles to deliver the drug to the site of infection, or obstruction. It has been shown that particles of three micra and above are taken out completely by the trachea, the bronchi, the bronchioles, and the alveolar ducts. Particles of one micron radius and greater are taken out by the lungs to the extent of 97 percent with only three percent recovered on expiration. Then, as the radius of the particle becomes

smaller yet, particles of 0.3 micron in radius are absorbed to the extent of only 35 percent and 65 percent recovery on expiration.[1] Similar figures have been confirmed by Van Wigh and Patterson in their work on dust laden air.[8]

The importance of particle size has been mentioned previously only in passing. In order to have the lungs retain a reasonable percentage of particles inspired, it is necessary that the particles remain above a given critical radius -- judged at present to be about 0.5 micron. The life period of a water droplet 0.5 micron in radius, under ordinary conditions of humidity, is only a fraction of a second. Examination of the mathematical theory of nebulization discloses that there are two essential factors which control the particle size and persistence of mists of aerosols. These variables are (1) the vapor pressure of the droplets and (2) the surface tension of the droplets. For example, the salt solution droplet evaporates until the increase of salt concentration reduces the vapor pressure sufficiently to prevent evaporation. Droplets of solutions which do not contain materials to lower the vapor pressure diminish rapidly in size after leaving the nebulizer and absorption is variable because of the unpredictable particle size distribution of smaller particles. Thus,

it has been shown that substances which lower the vapor pressure of the droplet sufficiently produce a more stable mist.[1] For nebulization therapy of the lungs, therefore, it is important to add a substance which stabilizes the particle size distribution. For practical purposes, glycerol is suitable. In addition to stabilizing the mist, glycerol reduces irritation and may retard absorption.

Now it may be seen that the various solutions used in aerosol therapy must be chosen carefully or modified with carriers to improve their efficiency. Since it is the purpose of this paper to deal with the stabilizing solutions of glycerin and propylene glycol, the therapeutic solutions will be mentioned only briefly. It was pointed out in the opening paragraphs that recently antibiotics have been incorporated into aerosol solutions. Also used, are vasoconstrictors to combat local mucosal edema, acute and chronic, as exists in allergic reactions or cystic fibrosis. Broncho-dilators are useful when smooth muscle spasm at the bronchiolar level complicates obstruction. The role of detergents in aerosol therapy is debatable and not to be considered here.

Glycerin finds a much wider use than that of aerosol stabilization. In fact, according to Lesser and Murphy[9], it is probably used more frequently in

prescriptions than any other substance except water. Any toxic properties it may possess are therefore of considerable importance. The ingestion of 30 milliliters of glycerol three times a day for forty days by normal human subjects was found to be harmless, but subcutaneous or intravenous injection of glycerol extracts may be followed by a local reaction or by edema.[10]

Glycerin is a viscous, colorless, odorless liquid with a neutral reaction and a sweetish taste. It is miscible in all proportions with water, alcohol, and chloroform but immiscible with ether, fats, and oils. Glycerin usually contains small amounts of water because of its hygroscopic property and when left exposed to air will absorb more than half its weight of moisture. It is readily absorbed from the GI tract, approximately 73 percent being absorbed in absorption of equimolar solutions of polyhydric alcohols. Absorption of these decreases with an increase in molecular weight. The rate of urinary excretion of glycerin depends upon a variety of factors such as the rate and mode of its introduction into the body, the composition of the diet, and the condition of the excretory organs. Drill's text of Pharmacology[11] states that in man, after oral doses of 200 grams of glycerin, as much as 50 grams may

be recovered from the urine, but after doses of two to three grams, only traces may be found. Excretion is complete by the end of six hours.

Propylene glycol, with properties similar to glycerin, affects the vapor pressure of the solution, reducing it and thereby prolonging the life of the droplet. Propylene glycol appears to have a synergistic effect with glycerin. The strength used should be about two to three times that of the glycerin used in order to have optimal effect. Propylene glycol is also useful due to its somewhat bacteriostatic effect in dilute concentrations. It is, according to Drill,[11] less toxic than glycerin and used as a solvent for oral medicine. The Pharmacopeia of the United States of America[12] describes propylene glycol as a clear, colorless, viscous liquid having a slightly acrid taste and practically odorless. It absorbs moisture when exposed to moist air. It is miscible with water, with acetone, and with chloroform in all proportions. It is also soluble in ether and will dissolve many essential oils, but is immiscible with fixed oils.

According to Drill,[11] propylene glycol is rapidly absorbed from the gastrointestinal tract. As much as 50 percent of a given dose has been recovered from the urine, and excretion may continue for as long as 24 hours.

The rate of disappearance from the body is roughly proportional to the amount in the body.

With the preceding paragraphs as an introduction into the general concepts of aerosol therapy and a few more specific remarks about glycerin and propylene glycol, it would now seem prudent to enter into the research aspect of this paper. The basis for the project arose from Abramson's[7] work with phenolsulfonphtholein aerosols in the standardization of nebulizers, and the long held, but little studied, theory that glycerin and propylene glycol stabilized particle size and thus increased the efficiency of aerosol therapy. Thus, it was the purpose of this project to determine if the absorption of PSP (phenolsulfonphthalein) into the blood by way of the pulmonary system was better when mixed in a 10 percent glycerin and 30 percent propylene glycol solution than when mixed in distilled water alone.

The procedure for this study was taken from Abramson[7] with certain modifications. The apparatus used included a DeVilbiss air pump and a Vaponephrine nebulizer. A "Y" tube was inserted into the rubber tubing between the pump and the nebulizer. PSP used was the 6 mg./1.0 cc. ampule. The media used with the PSP was either distilled water or a half-and-half mixture of 10 percent glycerin and 30 percent propylene glycol.

Dosage was established once for all tests run on children and again for the series run on adults. The child dose was established by starting the first subject on 1 cc. PSP, obtaining his weight in kilograms (34.2 Kg.), and then calculating a dosage of .175 mg. PSP per Kg. body weight. The adult dose was calculated similarly by giving the first subject 1 cc. PSP, obtaining his body weight in kilograms (78 Kg.), and then calculating a dosage of .077 mg. PSP per Kg. body weight.

The correct dosage for the subject was put into the nebulizer with an equal amount of distilled water or the glycerin and propylene glycol mixture. The subject drank 500 cc. of water and voided immediately prior to starting inhalation. Inhalation was then accomplished by putting the nebulizer into the mouth and placing the finger over the "Y" tube at the same time inhaling through the mouth. (Nose clamps could be used if needed to insure complete mouth breathing.) The finger was removed with every expiration, thus insuring delivery of the dye only with inspiration. Total breathing time varied from 10 to 20 minutes depending on dosage and subject.

Upon completion of inhalation, the residue dye in the nebulizer was rinsed out completely with distilled water into a 100 cc. volumetric flask and saved.

Hourly urine samples were then collected -- the entire specimen in each case. These, as well as the residue, were treated like any normal PSP Kidney Function Test.[13] Samples were alkalinized with 10 percent sodium hydroxide to bring out the color of PSP, diluted to any fractional volume of 1000 cc. and read on a Coleman Jr. Spectrophotometer. A distilled water blank was used for the zero setting and a standard of 1 cc. PSP (6 mg.) in 10 cc. sodium hydroxide and diluted to 1000 cc. with water used to enable calculation of PSP in urine.

Calculations:

$$\frac{\text{Reading of standard}}{\text{Reading of unknown}} \times \frac{\text{Dilution of unknown}}{\text{Dilution of standard}} = \%\ \text{dye excreted}$$

Percent dye excreted X 6 = mg. of dye excreted since the standard contained 6 mg. PSP.

The longest series of tests run on any group of subjects was an adult series of twenty done with L.M. and P.B. In addition to the use of water and glycerin-propylene glycol inhalation, the subjects also mixed their dosage of PSP in the 500 cc. of water normally drunk prior to inhalation. This was done to test absorption into the blood from the gastro-intestinal tract as compared to pulmonary vascular absorption. Dosage for L.M. was 1 cc. PSP and dosage for P.B. was 0.95 cc. PSP. Weights of the subjects were 78 Kg. and 74 Kg. respectively. (Table 1)

TABLE 1

ADULT SERIES - 1

		Glycerin		Water		Oral	
		LM	PB	LM	PB	LM	PB
1st Hour	Test 1	.498	.480	.440	.367	.210	.202
	Test 2	.520	.380	.250	.420	.200	.160
	Test 3	.339	.540	.350	.373	.090	.086
	Test 4	.339	.550	.367	.307	.210	.171
	Test 5	.443	.476	.200	.440	.228	.208
	Test 6	.350	.438	.400	.400	.280	.172
2nd Hour	Test 1	.363	.346	.267	.250	.300	.208
	Test 2	.283	.320	.327	.346	.227	.208
	Test 3	---	---	---	---	.080	.107
	Test 4	.267	.400	---	.260	.294	.153
	Test 5	.420	.482	.270	.343	.267	.158
	Test 6	.517	.386	.280	.257	.070	.200
3rd Hour	Test 1	.200	.160	.253	.207	.160	.140
	Test 2	.200	.193	.168	.227	.167	.087
	Test 3	.500	.520	.533	.410	.107	.107
	Test 4	.227	.213	.533	.213	.200	.174
	Test 5	.240	.193	.197	.193	---	.103
	Test 6	.210	.217	.197	.200	.175	.150

Figures given in mg. PSP

Results of all tests run on adult subjects using three routes of administration -- oral, water inhalation, and glycerin-propylene glycol inhalation. Readings were made on first, second, and third hour urine samples only.

The next longest series was done on a child, M.K., whose weight was 24 Kg. and whose dosage, calculated at 0.175 mg./Kg. body weight, was 4.2 mg. or 0.7 cc. PSP. (Table 2)

The second child series was done on subject S.K., who weighed 46 Kg., and on the child dosage as stated above, received 1.35 cc. PSP. (Table 3)

Subject H.G. weighed 34.2 Kg. and received 1 cc. PSP (6 mg.). It was this subject on whom the child dosage of 0.175 mg./Kg. of body weight was calculated. (Table 4)

A few items of miscellaneous data were taken to aid in evaluating the accuracy of the readings.

(a) Non-alkalinized and non-diluted urine was read on the spectrophotometer against a distilled water blank and gave a reading of .006 optical density (O.D.). This urine volume was 180 cc. so had a reading corresponding to .036 mg. PSP. This value would vary with urine concentration, however.

(b) The residue of the nebulizer was always diluted to 100 cc. and had an O.D. of approximately .180 or 0.6 mg. PSP. This was fairly constant regardless of the initial volume in the nebulizer.

It should be mentioned that none of the series listed should be compared with any other. As previously stated,

TABLE 2

CHILD SERIES - 1
(M.K.)

		Glycerin	Water	Oral
First Hour	Test 1	.198	.040	.200
	Test 2	.066	.066	.060
	Test 3	.125	.280	.227
	Test 4	.250	.040	---
Second Hour	Test 1	.193	.150	.167
	Test 2	.140	.050	.154
	Test 3	.093	.127	.154
	Test 4	.214	.134	---
Third Hour	Test 1	.063	.210	.097
	Test 2	.127	.134	.167
	Test 3	.067	.084	.110
	Test 4	.183	.063	---

Figures given in mg. PSP

Results of all tests run on child subject M.K. using three routes of administration -- oral, water inhalation, and glycerin-propylene glycol inhalation. Readings were made on first, second, and third hour urine samples only.

TABLE 3

CHILD SERIES - 2
(S.K.)

		Glycerin	Water	Oral
First Hour	Test 1	.666	.433	.666
	Test 2	.450	.533	.233
Second Hour	Test 1	.300	.273	.240
	Test 2	.216	.375	.280
Third Hour	Test 1	.217	.226	.183
	Test 2	.460	.346	.226

Figures given in mg. PSP

Results of all tests run on child subject S.K. using three routes of administration -- oral, water inhalation, and glycerin-propylene glycol inhalation. Readings were made on first, second, and third hour urine samples only.

TABLE 4

CHILD SERIES - 3
(H.G.)

		Glycerin	Water	Oral
First Hour	Test 1	.241	.165	.139
	Test 2	.183	.216	---
Second Hour	Test 1	.198	.162	.150
	Test 2	.415	.198	---
Third Hour	Test 1	.113	.108	.132
	Test 2	.332	.173	---

Figures given in mg. PSP

Results of all tests run on child subject H.G. using three routes of administration -- oral, water inhalation, and glycerin-propylene glycol inhalation. Readings were made on first, second, and third hour urine samples only.

the adult dosage differs from that of the child and also the dosage differs for each of the three child series. The absolute value of the PSP excreted, in milligrams, likewise should not be considered very indicative, but rather the comparison of the value between oral, water, or glycerin and propylene glycol in any one subject.

It was discovered between Child Series 1 and Child Series 2 that a precipitate formed in the urine upon the addition of the 10 percent sodium hydroxide and this precipitate was responsible for the high reading in Series 2 and 3. To forestall this abnormally high reading, the urine samples were alkalinized with 10 percent sodium hydroxide as before, diluted with water, read on the spectrophotometer, then filtered through Number 42 filter paper and read on the spectrophotometer again. A tabulation of 26 readings was done for subject L.M. and also for subject P.B. in the adult series where readings before and after filtration were taken. The "filtered reading" was subtracted from the "non-filtered reading", each in mg. and in all 26 readings with both subjects, none of the differences exceeded 0.1 mg./100 cc. final volume. Average difference for the 26 readings of subject L.M. was .082 mg./100 cc. and for subject P.B. was .043 mg./100 cc. It should be noted, that, on a

comparative basis, as long as the entire series was filtered or was not filtered, the figures are still valid. The above mentioned differences before and after filtration are useful only if use is made of the absolute value of the figures.

An attempt was made to determine the cause of the precipitate. A check with clinical pathologists revealed that precipitates had never interfered with a normal PSP Kidney Function Test. The only difference between normal laboratory tests and this test was the partaking of meals. Gradwohl[13] states that the subject should not eat prior to the test. Since the subjects of this test were used several days in succession, a restriction of meals was not practical. It was theorized that the precipitate was due to a postprandial alkalinity with phosphates precipitating out. It was thought that 10 cc. of 10 percent sodium hydroxide was in excess of that required to bring out the color of the PSP. A drop-by-drop addition of base to subsequent samples revealed the precipitate forming as soon as the red color of the PSP appeared.

An attempt was made to establish a time relationship for the formation of the precipitate but this was too variable to be indicative. On one day, subjects L.M. and P.B. in the adult series ate no breakfast prior to

inhaling the PSP and no precipitate formed in the first three hourly urine samples. Subsequent hourly samples did show a precipitate but the subjects drank coffee in the interim so this may have been responsible.

The PSP standard was filtered on two different occasions to ascertain if any PSP was lost by filtering the urine samples. In each case, the standard had the same optical density before and after filtration. It was found, however, that normal non-alkalinized urine gave a lower reading after filtration (.117 to .073 mg./ 100 cc.) indicating that other urinary constituents besides PSP add to the O.D. reading of the samples.

Another possibility of the test variation was that one of the PSP substrates might give a more prolonged absorption than the other. To check this, six and seven hourly urine samples were collected to see if the reading formed a curve. Figures 6 and 7 show that all three methods of administration have similar downward trends and all at approximately the same level. It must be remembered, however, that this was a one-time test and not a series. Thus, if a similar test were repeated there would be variations just as between the two adults. The chief significance of such a test lies in illustrating that excretion from all three sources is continued for a long period. Secondly, after the first 2 or 3 hours, the

TABLE 5

ADULT SERIES - 2

	Glycerin		Water		Oral	
	LM	PB	LM	PB	LM	PB
First Hour	.498	.480	.440	.367	.210	.202
Second Hour	.363	.346	.267	.250	.300	.208
Third Hour	.200	.160	.253	.207	.160	.140
Fourth Hour	.220	.226	.250	.183	.210	.100
Fifth Hour	.087	.232	.263	.186	.120	.083
Sixth Hour	.117	.126	.114	.107	.093	.060
Seventh Hour	---	---	.127	.103	---	---

Figures given in mg. PSP

Results of one test by each of the three routes of administration. Readings were made on each of seven hourly urine specimens.

Figure 6 - Adult L.M.

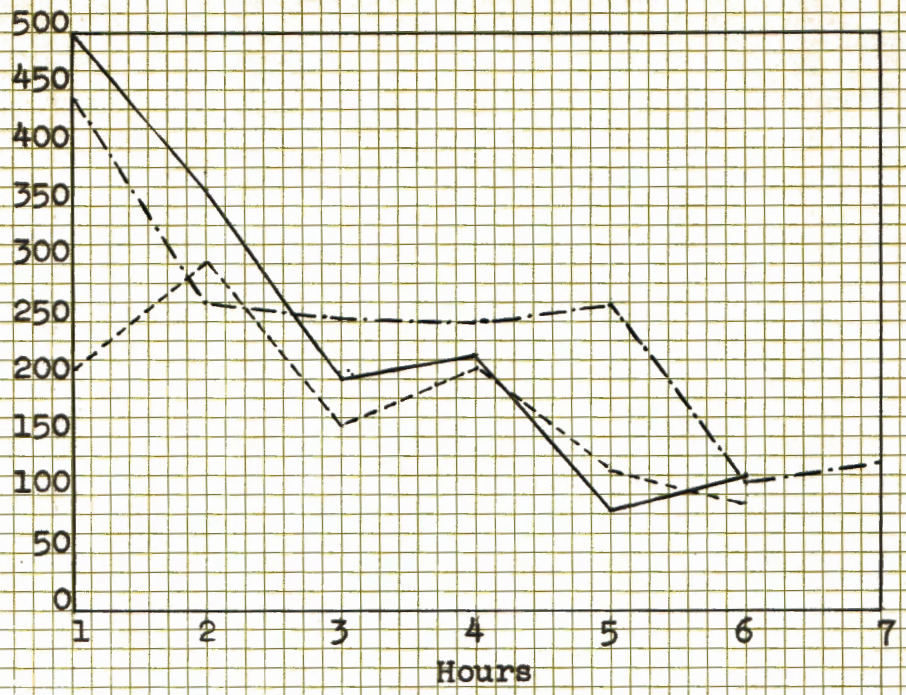
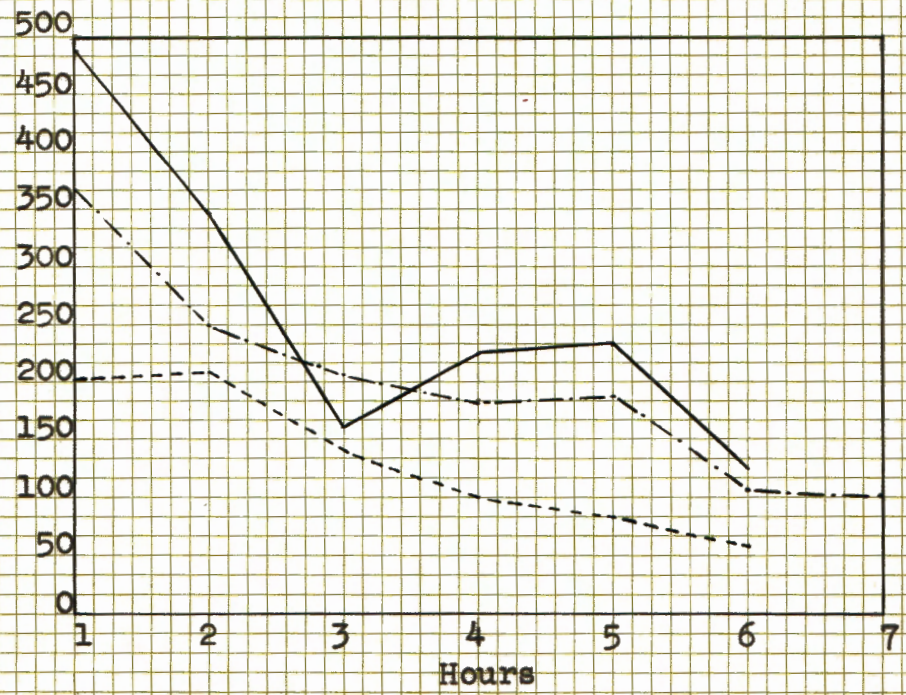


Figure 7 - Adult P.B.



Comparison of PSP Excretion of three different administrations over 7 hour period. Figures are given in thousandths of milligrams.

LEGEND:
_____Glycerin-Prop.Glycol
_._._Water
------Oral

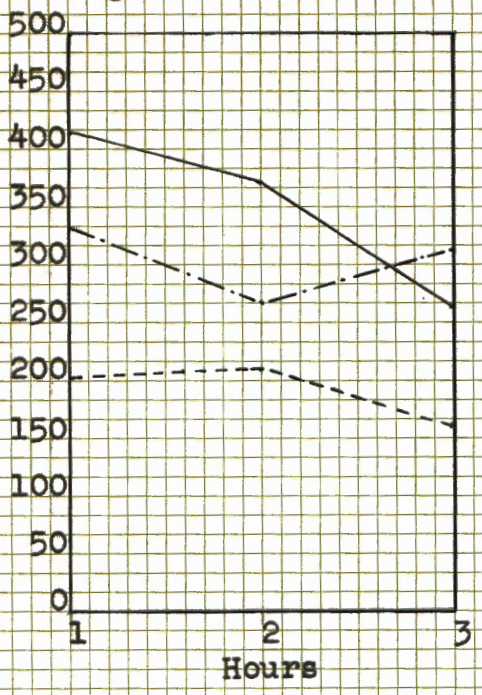
variation between the three sources fluctuates and is non-significant.

Figures 1 and 2 of the adult series illustrate, in part, the whole purpose of this experiment. They show that for the first two to three hours, at least, absorption into the blood of PSP in a glycerin and propylene glycol media appears to be considerably better than either water or oral, and the water much higher than the oral.

Figures 3, 4, and 5 for the Child Series 1, 2, and 3 are not as conclusive as those for the adult series. Water still is poorer than glycerin and propylene glycol, but for some obscure reason, one of the three series for oral administration shows an unusually high value for oral absorption. (Table 3)

It should be noted that of the 71 tests run on eight different subjects, no toxic reactions of cough, fever, or weakness occurred, as mentioned by Abramson.[7] However, the toxic reactions he noted were with larger concentrations of the dye. Apparently the reaction noted was due to the dye rather than the glycerin, since Abramson, in an article dealing with the use of glycerin,[14] reports that high concentrations of glycerin apparently do not lead to any irritation of the lungs. He states that from 10 to 50 percent glycerin has proved serviceable and has been used fairly regularly for one year by eight

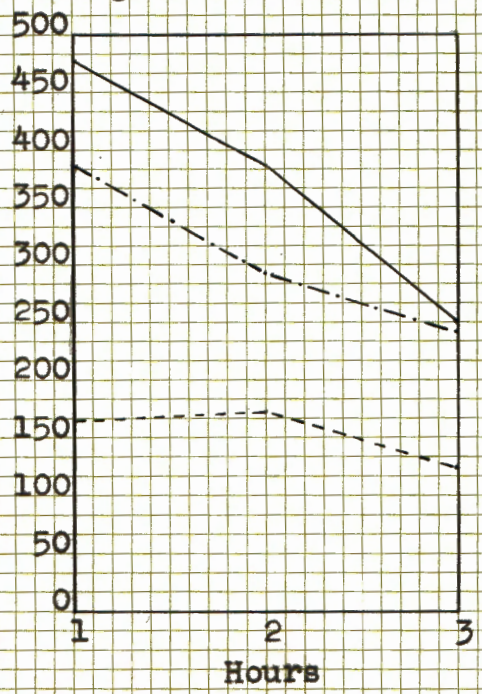
Figure 1 - Adult L.M.



Comparison of PSP Excretion of three different administrations over a 3 hour period.

(Figures for PSP excretion given in thousandths of milligrams and are means of all tests for each of three hours.)

Figure 2 - Adult P.B.



LEGEND:

_____ Glycerin-Prop. Glycol

_._._. Water

------ Oral

Figure 3 - Child M.K.

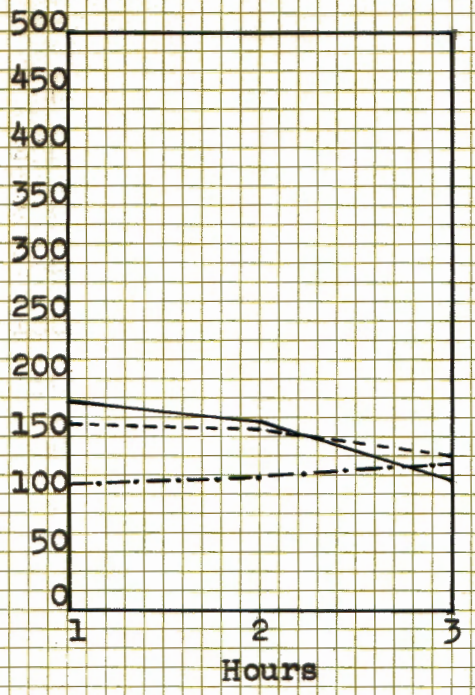


Figure 4 - Child S.K.

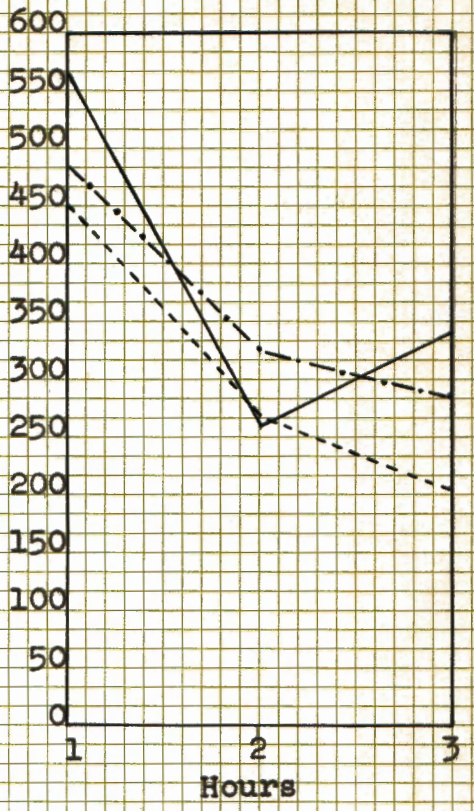
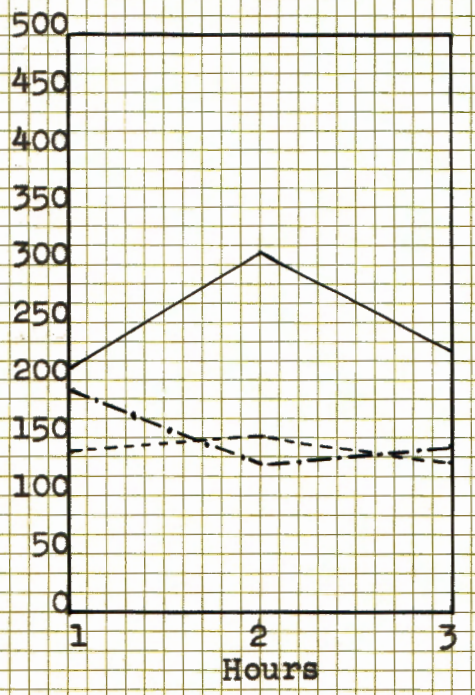


Figure 5 - Child H.G.



Comparison of PSP Excretion of three different administrations over a 3 hour period.

(Figures for PSP excretion given in thousandths of milligrams and are means of all tests for each of three hours.)

LEGEND:
____ Glycerin-Prop.Glycol
_·_·_ Water
\- - - - Oral

intelligent people who found normal commercial aqueous solutions difficult to take. He does believe that more than 10 percent glycerin is required for suitable effects. Thus, it would appear that glycerin is a non-causative factor in the reactions noted above.

Finally, it would seem to be of interest to explain some of the variability in the results obtained. It is the author's opinion that the wide range of values in the child series is due to technique rather than significant differences in absorption. The ages of the six different child subjects varied from 5 years to 13 years. All were hospital patients with diagnoses completely unrelated to pulmonary, vascular, or renal disease. All learned the technique of deep breathing with the Y-tube and all improved with each test. Still, they exhaled more dye, breathed less deeply, swallowed more dye, and in general provided a greater inefficiency in technique than did the adults. Also, because there was less chance to err, the oral absorption and excretion values more nearly approached the inhaled method in the child series.

Overall comparison of the oral and inhaled routes of administration require certain considerations. For instance, since the dye by oral route was mixed in 500 cc. of water, there was little deposition of dye on the mucosal surfaces of the mouth and gastro-intestinal tract

prior to absorption with a resultant more dye presented to the stomach for absorption. As was reported earlier, it is known that nearly 75 percent of oral glycerin solution is absorbed in the gastro-intestinal tract. The pulmonary tree, on the other hand, presents a greater surface area for accumulation of dye prior to its reaching areas where it will be absorbed and this in turn is in a stronger relative concentration than that given orally. Finally, approximately 10 percent of the dye in the inhalation method was left in the nebulizer whereas only insignificant amounts were left in the container used for oral intake.

SUMMARY

This is a comparative study of pulmonary absorption of a glycerin-propylene glycol solution or water in 71 tests on children and adults. Phenolsulfonphthalein (PSP) was used in each case as the indicator, the results obtained by spectrophotometric determinations. In addition to comparing pulmonary absorption of these two, the PSP in water was also ingested orally to determine absorption from the gastro-intestinal tract. Of the 71 tests, 36 were on two adult subjects and 35 on child subjects.

The solution was inhaled through a nebulizer and then hourly urine samples collected to be tested for the

quantity of PSP contained. Similar urine collections were made after oral ingestion of the dye. Dosage was determined for each subject on a mg./Kg. basis.

Variables were felt to have a direct bearing on results and thus worthy of consideration. Technique of inhalation varied with age and number of previous tests on the child subjects thus altering the amount of solution reaching the pulmonary tree. A troublesome precipitate developed, which, after filtration and repeated calculations, was thought not to alter the final comparative results, affecting all three routes of administration similarly.

Results of the tests were two-fold. First, it was shown that PSP is continually filtered in the urine for some period of time. One test for each of the 2 adult subjects was continued for seven hours with each of the routes of administration and appreciable amounts of PSP were still appearing in the urine at the end of that time. It was noted, however, that after three hours the amount excreted was so variable that results were inconclusive. It was for this reason that all tests were run only on three hour urine specimens. Secondly, as may be seen from the accompanying charts and graphs, there was a marked difference in urinary excretion of PSP for each of the three routes of administration. With all subjects,

the inhaled solution of glycerin and propylene glycol resulted in the greatest quantities of dye returned, followed by inhalation of the dye and water solution. The oral ingestion of the dye in water produced the poorest returns at the end of three hours.

Finally, it should be noted that none of the subjects developed unfavorable reactions to either the dye or the glycerin-propylene glycol solution. No other complications were noted.

CONCLUSIONS

From the data so far obtained, it appears that the best pulmonary absorption of the dye occurs with the glycerin-propylene glycol mixture. Also, due to reasons previously stated, absorption from the gastro-intestinal tract is thought to be considerably less.

Thus, we conclude that a glycerin-propylene glycol mixture does in fact stabilize the aerosol mixture in some way so that more aerosol is presented deeper within the pulmonary tree and there deposited where it does the most good. Therefore, it would seem desirable to add such a mixture to antibiotics, mucolytic enzymes and other therapeutic drugs which can be nebulized and used in the treatment of the various pulmonary diseases.

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