CHEMICAL AND CLINICAL ASPECTS OF SODIUM PERBORATE THERAPY.*,[1]

BY L. L. MANCHEY AND S. LEE.

The wide-spread use of sodium perborate as an adjunct in the treatment of Vincent's infection and in related conditions has brought to the attention of the dental and medical professions certain attending untoward effects. Bloodgood (1), who in 1910 suggested its use in the treatment of Vincent's infection, later reported (2) that too frequent treatment produces an irritation. Hirschfeld (3) has attributed a number of cases of chemical burns, slight edema of the lips and instances of hairy tongue to the too frequent use of sodium perborate preparations.

The undesirable effects from the drug have been ascribed variously to a number of possible causes: to impurities present in the compound, such as sodium hydroxide (4); to sodium hydroxide regarded not as an impurity but as a hydrolytic product of the parent compound (2); to prolonged contact of undissolved salt with the oral tissues through failure to remove it by adequate rinsing (2); to individual idiosyncrasy to the compound (4); to essential oils used as flavoring agents.

Interest appears to have centered in particular in alkalinity as the cause of the ill effects. In this connection, the following equations adapted from Mellor's Comprehensive Treatise (5) have been cited elsewhere (1) as an illustration of the theoretical decomposition of sodium perborate in water to sodium hydroxide and other products.

$$4NaBO_3 + 5H_2O \rightarrow 4H_2O_2 + 2NaOH + Na_2B_4O_7$$
$$Na_2B_4O_7 + H_2O \rightarrow 2HBO_2 + 2NaBO_2$$
$$2NaBO_2 + 2H_2O \rightarrow 2HBO_2 + 2NaOH$$

The circumstance that Vincent's infection is caused supposedly by the anærobic Vincent's fusiform bacillus and spirillum existing either in symbiosis or as varied forms of the same organism leads *a priori* to the commonly accepted view that the value of the compound as a drug depends upon the release of oxygen when it is brought in contact with the affected tissue. Indeed, the implication in the majority of allusions to its therapeutic application is that the oxygen which is lost in gaseous form, rather than the active oxygen, manifests the virtue of the compound. This attitude is difficult to reconcile with the antibacterial properties of hydrogen peroxide (6), (7), which is less efficient in the presence of certain kinds of organic matter where the decomposition and liberation of oxygen is greatly accelerated.

According to the U. S. P. XI, the salt is soluble at 25° C. to the extent of 1 Gm. in about 40 cc. of water, and by definition should contain not less than 9 per cent of available oxygen. In view of the U. S. P. data for solubility and the minimum permitted available oxygen content it is doubtful whether, under the conditions of use, the total dissolved available oxygen representing both undecomposed sodium perborate and the hydrogen peroxide ever greatly exceeds 0.3 per cent.

The decomposition of sodium perborate to yield hydrogen peroxide is greatly accelerated by acids or acid salts and the rate of solution and apparent solubility

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* Scientific Section, A. Ph. A., New York meeting, 1937.

[1] From the research laboratories of Vick Chemical Company, New York, N. Y.

are noticeably increased. By carefully adjusting the proportions and concentrations of perborate and acid, the p_H of their aqueous solutions may be brought within desirable limits for use in the mouth, while by limiting the amount of water the dissolved available oxygen is increased many fold above that of saturated solutions of sodium perborate. Thus while the objections which weigh most heavily against the use of sodium perborate, *viz.*, its high alkalinity and the possibility of retaining undissolved salt in contact with the oral tissues have been surmounted, greater flexibility in the hydrogen peroxide concentration is made possible to suit the peculiarities of individual requirements.

Numerous reports (5), (8), (9), (10), (11) have appeared in the literature that solutions of higher available oxygen content may be obtained with sodium perborate by the addition of tartaric, citric, boric and other acids.

Whereas the significance of such common acids in conjunction with sodium perborate was well understood, it was not until the greater adaptability of monocalcium phosphate for dental and oral applications was brought to our notice[1] that its probable superior merit was considered.

In contradistinction to the organic acids, the phosphate may be credited with the advantage of affording by reaction with sodium perborate insoluble phosphates of calcium. Mixtures of sodium perborate and monocalcium phosphate for cleaning the teeth thus combine a certain degree of mechanical cleansing with the advantages of higher concentrations of available oxygen in solution. Such mixtures may find use, therefore, either as tooth powder or mouth rinse.

The intent of this investigation has been to determine the flexibility of the perborate-phosphate composition in relation to p_H and to stability; and to ascertain the relations between composition and effects upon the oral tissues. In the preparation of the perborate-phosphate mixtures, sodium perborate was used in the form of monohydrate instead of U. S. P. tetrahydrate.

EXPERIMENTAL.

The indicator strip method, according to Wulff (12), (13) was employed in the determination of p_H. It combines the simplicity of colorimetric methods with applicability to opaque or colored mixtures, and is, moreover, within the limits of precision required by the practical aspects of our studies. The technique followed involved a slight departure from the procedure recommended for alkaline solutions. The modified method is as follows: An indicator strip covering the desired range is subdivided into small pieces about 4 x 8 mm. One of the pieces is folded by means of a blunt-tipped forceps through the middle to form a "V" and is then placed directly on the scale holder with the color standard adjusted. Two drops of the test liquid are placed on the "V" strip which is then covered quickly with a microscope slide to prevent absorption of carbon dioxide and acid vapors from the atmosphere. Care is exercised that the microscope slide is not pressed too tightly against the indicator strip to cause it to flatten and become fixed against one of the opposing glass surfaces; otherwise the liquid is not free to permeate both sides of the strip, and the time for the indicator change is unnecessarily prolonged.

By oscillating the slide on one of its ends held against the pane of the scale holder as a fulcrum adequate circulation of liquid is ensured. By this method, the color changes may be followed directly with the eye without the uncertainty experienced by the operator of over- or under-exposing the strips by the usual method. Despite the contact between liquid and air engendered by the oscillations, mixtures such as the ones investigated here are sufficiently buffered to eradicate the effects of atmospheric carbon dioxide.

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[1] Dr. Paul Poetschke.

In the discussion which follows, the values given for p_H, unless otherwise qualified, represent measurements made at room temperature at a predetermined contact time between water and powder following which there were shown to be no further fluctuations in the acid-base equilibrium. A fifteen-minute interval was shown experimentally to provide adequate time for equilibrium to be established. This was demonstrated by following the change in p_H with time to a constant value in suspensions of 5 Gm. of variable composition mixtures of sodium perborate monohydrate and mono-calcium phosphate in 100 cc. of distilled water.

With pure perborate either as monohydrate or as tetrahydrate the value remained unaltered at 10.3 between 15 minutes and 48 hours following the introduction of the powder into the water. Concentration of the perborate in water of 10, 15 and 20 per cent $\left(\frac{W}{W}\right)$ did not affect the reading. For pure monocalcium phosphate, however, the value dropped from 3.8 in 15 minutes to 3.4 in 48 hours; nor were constant readings obtained in 15 minutes with mixtures of the two in which the monocalcium phosphate was present in excess of 65 parts per 100 parts of mixed powder. This is without doubt explained by the presence of phosphate in excess of the amount required to effect complete decomposition of the perborate and to the relatively slower solution rate of the phosphate in the absence of perborate. Mixtures containing less than 65 per cent of monocalcium phosphate afforded constant readings in less than 15 minutes.

Presumptive of the dual applicability of a properly adjusted mixture for use either as a powder on the brush or as a rinse in higher dilution, the p_H-composition relation was followed in suspensions of the mixtures in water at two levels representing tentatively adopted limits of concentration. The proportions used were 4 Gm. of mixture to 100 cc. of distilled water for the weak suspension and 5 Gm. of mixture to 10 cc. of distilled water for the more concentrated form. The procedure was to stir the mixture of powder and water frequently during 10 minutes, allow 5 minutes for sedimentation and then determine the p_H following the modified method described above. The results are depicted graphically in Fig. 1. It is evident from the curve illustrating the more concentrated suspension that the acid-base equilibria within the composition range 40 parts sodium perborate: 60 parts monocalcium phosphate and 60 parts sodium perborate: 40 parts monocalcium phosphate lie approximately within the extreme limits of p_H reported for saliva from healthy normal subjects. Starr (14) found the reaction to vary from p_H 5.75 to 7.05.

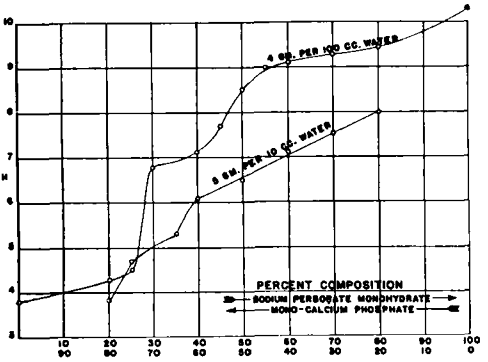

Fig. 1.

The upper curve shows that in higher dilution, within the same range, the alkalinity of sodium perborate has been significantly lowered.

Consequently the limits $^3/_2$ and $^2/_3$ were placed upon the perborate/phosphate composition ratio of mixtures used in preliminary tests to ascertain their effects in comparison with sodium perborate upon the oral tissues. The clinical phases of the investigation will be found more fully described toward the close of the report.

Stability of Sodium Perborate at High Humidity in the Presence of Monocalcium Phosphate.—Into a series of vials $^7/_8$ x $2^1/_2$ inches were weighed separately varying amounts of sodium perborate monohydrate and monocalcium phosphate, so that the combined weights amounted to approximately 0.5 Gm. The components were thoroughly mixed by rotating the vials, which were then placed in an upright position in a humidor over diluted sulfuric acid affording at 25° C. a relative humidity of 75.6%. Periodically, vials were selected according to sodium perborate content and assayed for available oxygen by the U. S. P. XI method. In Fig. 2 is shown the loss in available oxygen occurring in the samples over a storage period of 40 days. The sodium perborate monohydrate used in these mixtures originally assayed 14.8% available oxygen. The graph clearly shows that the stability of the perborate is greatest in the presence of limited amounts of monocalicum phosphate.

It seemed a reasonable assumption that sodium perborate monohydrate would afford more stable mixtures with an anhydrous or partially dehydrated form of monocalcium phosphate than with the usual commercial monohydrates.

This assumption appeared even more plausible when it was shown that the tendency to cake was definitely less in mixtures with the dehydrated form. The observations were made upon mixtures for which the perborate/phosphate ratio of one group was $^3/_2$ and for a second group, $^2/_3$. Equal amounts of the mixtures were exposed to an atmosphere of high moisture content under identical conditions of temperature, humidity, surface area and time.

As a more decisive test, bulk samples, representing three tentative formulas, each containing the same per cent and form of sodium perborate, but differing in perborate/phosphate ratios and in the character of the monocalcium phosphate were kept in dentifrice cans fitted with composition screw-cap closures and later assayed for deterioration of sodium perborate. Included in the formulas were flavoring oils and sufficient polishing agent (tricalcium phosphate), chemically indifferent to the perborate and monocalcium phosphate, to make a total of 100 parts of finished product. The quantity of polishing agent varied in the samples according to their perborate/phosphate ratios. The sodium perborate employed for this purpose was in the form of monohydrate, milled to a No. 150 average mesh, and assayed 15.0 per cent available oxygen after milling. Other characteristics of the finished mixture are given in Table I.

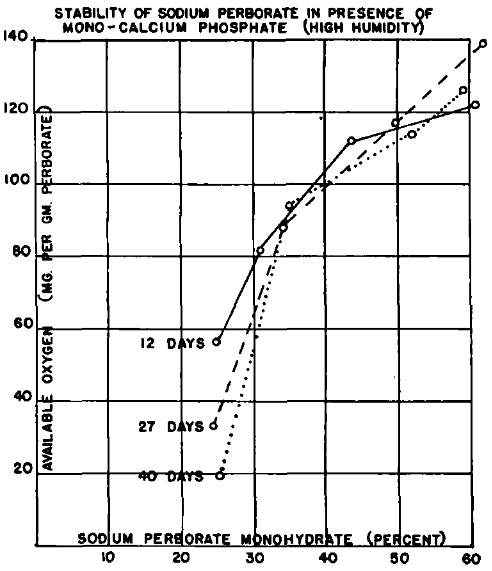

Fig. 2.

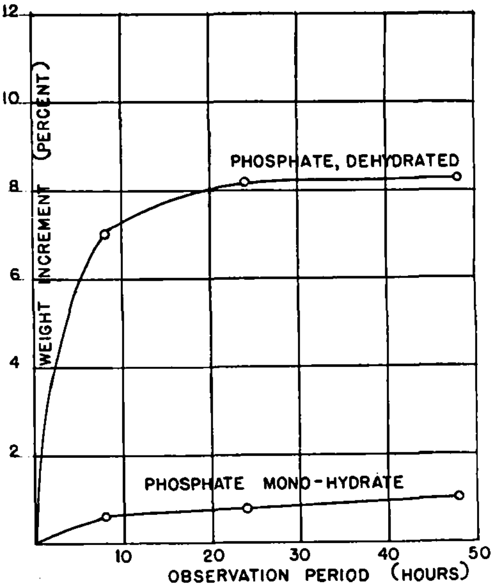

Fig. 3.

TABLE I.—CHARACTERISTICS AND EFFECTS OF STORAGE AT HIGH HUMIDITY AND TEMPERATURE.

Sample.	Ratio Perborate/ Phosphate.	Per Cent Perborate Mono-hydrate.	pH.*	Per Cent Original Available Oxygen.	Per Cent Loss in Total Available Oxygen.	
					Humidity—88.5 Per Cent Temp.—100° F., Days—22.	Humidity—88.5 Per Cent Temp.—Room, Days—22.
40	0.66	30	6.6	4.60	16.7	4.5
41	1.25	30	7.2	4.62	26.0	4.3
42	1.20	30	7.1	4.64	33.6	14.2
Sodium Perborate Tetrahydrate				10.05 to 10.20	70.0	20.0

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* Determinations made 15 minutes after suspending 5-Gm. samples in 10 cc. distilled water.

Both Samples 40 and 41 contained the dehydrated form of monocalcium phosphate. The regular monohydrate was used in Sample 42. Screening analyses gave for the dehydrated form, 95 per cent; and for the monohydrate, 98 per cent through a No. 200 mesh screen. The conditions of storage are indicated in the table. A well-known brand of sodium perborate tetrahydrate similarly packaged was included under each condition of test.

The figures reported for loss in available oxygen show that the perborate is more stable in the presence of dehydrated phosphate, under the conditions of test, than in the presence of the monohydrate; that under the conditions indicated, tetrahydrated sodium perborate loses more of its available oxygen per gram than its monohydrate in the presence of sufficient monocalcium phosphate, either as monohydrate or the dehydrated form, to nearly neutralize the alkalinity of the perborate.

It is worthy of mention that the affinities of the two forms of phosphates for moisture run more or less parallel with their influence upon the stability of the perborate. In Fig. 3 it will be seen that the rate of moisture absorption is greater for the dehydrated phosphate. This data was obtained by exposing quantities of the phosphates to a humid atmosphere to constant weight. Approximately one Gm. of the phosphates, accurately weighed, was spread out uniformly on two-inch watch glasses and placed at room temperature over diluted sulfuric acid, affording at 25° C. a relative humidity of 75.6 per cent.

Differences in the neutralization rates with Samples 40, 41 and 42 are suggested by the figures shown in Table II.

TABLE II.—CHANGE IN p_H OF AQUEOUS SUSPENSIONS.

Minutes.	Sample 40.	Sample 41.	Sample 42.	Sodium Perborate Tetrahydrate (U. S. P.).
1	6.7	7.3	7.5	10.2
2	6.6	7.3	7.4	10.3
4	6.6	7.2	7.3	10.3
7	6.6	7.2	7.2	10.3
10	6.6	7.2	7.1	10.3
15	6.6	7.2	7.1	10.3
30	6.6	7.2	7.1	10.3

The p_H values given are for readings taken at intervals on suspensions of 5 Gm. of mixture in 10 cc. of distilled water. It will be seen that whereas the perborate/phosphate ratio for 41 (dehydrated phosphate) is slightly greater than that for 42 (monohydrate) the rate of neutralization is greater, and the time for reaction to be completed is less. These distinctions must be attributed to the difference in the physical characteristics of the phosphates.

EFFECTS UPON ORAL TISSUES.[1]

The initial tests conducted in connection with this phase of the investigation were intended to reveal whether under similar conditions of application, sodium perborate, U. S. P. XI, and mixtures of sodium perborate monohydrate with monocalcium phosphate would produce inflammatory reactions in contact with the oral tissues. For this purpose small cotton cloth bags of dimensions $3^1/_2$ x $2^1/_2$ cm. and containing 0.75 Gm. of the test material were placed between the gum and lip of the lower jaw of human subjects. Two perborate-phosphate mixtures, representing, respectively, perborate/phosphate ratios of $^3/_2$ and $^2/_3$, were applied in conjunction with U. S. P. perborate to the gums of a number of individuals in the manner described. When retained *in situ* for 30 minutes, the U. S. P. perborate produced erythema, edema and in some instances vesication of the tissues in direct contact with the poultices. With the mixtures, the results in general were the same except that there seemed to be a greater tendency toward stimulation of tissue circulation

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[1] These studies were conducted by Joseph Schroff, M.D., D.D.S.

with less necrosis and sloughing. Burning sensations on the lip and tip of the tongue were noted also. The degree of discomfort varied according to the time the poultices were held in place. Individual variations were observed, but the same persons responded to repeated tests in the same manner.

The effects noted in the instance of the perborate-phosphate mixtures were attributed to the high concentration of hydrogen peroxide formed by reaction at the site of contact between tissue and poultice under conditions such that the volume of fluid was small as compared with the test material. A similar conjecture could hardly explain the effects from U. S. P. perborate where, as has been previously suggested, the hydrogen peroxide concentration is limited by the low solubility of the salt.

In a second series of tests conducted in a similar manner with poultices of perborate-phosphate mixtures having a perborate/phosphate ratio of 1.22, but with sufficient added inert material to reduce the perborate concentration in three different mixtures to 10, 20 and 30 per cent of perborate monohydrate, respectively, inflammatory reactions on the mucous membrane of the mouth were negligible. Only restricted areas of hyperemia or very slight discomfort were produced in a few individuals by the 30 per cent mixture. No reactions were elicited by the 10 and 20 per cent perborate mixtures; nor was any change in the response caused by decreasing the perborate ratio in the 30 per cent mixture from 1.22 to 1.0. This alteration in perborate/phosphate ratio corresponds to a change in p_H of from 7.4 for the 1.22 ratio to 6.6 for the 1.0 ratio. Concurrent with the poultice tests made with the material represented by the 1.0 ratio, control tests were made on the same and different individuals with a mixture containing no monocalcium phosphate, but with sufficient inert material to give a perborate concentration of 30 per cent. Soreness and severe inflammation of the tissues were caused only by the control mixture.

SUMMARY AND CONCLUSIONS.

1. Monocalcium phosphate has been shown to reduce effectively the alkalinity of sodium perborate, thereby removing a common objection to its use in the treatment of Vincent's infection and allied conditions.
2. Neutralization is sufficiently rapid to be of practical importance in dental therapeutic applications.
3. Insoluble phosphates of calcium are formed by reaction between sodium perborate and monocalcium phosphate which are of value in a dentifrice because of their mechanical cleansing properties.
4. Monocalcium phosphate augments the solution rate and the apparent solubility of sodium perborate so that the benefits of the potential water-soluble available oxygen may be more quickly and more fully realized.
5. If stored under conditions approximating the maximum humidity and temperature of any climate, sodium perborate tetrahydrate (U. S. P.) has been shown to be less stable than sodium perborate in the form of monohydrate when 30 parts of the latter are mixed with from 20 to 37.5 parts of dehydrated monocalcium phosphate and sufficient tricalcium phosphate to make 100 parts.
6. Sodium perborate tetrahydrate (U. S. P.) has been shown to cause harmful effects when applied to the gums of normal healthy human subjects.

7. Similar harmful effects were caused by a mixture of 30 parts of sodium perborate monohydrate and 70 parts of inert tricalcium phosphate.

8. No harmful effects were caused by a mixture of 30 parts of sodium perborate monohydrate, 45 parts of dehydrated monocalcium phosphate and 25 parts of inert tricalcium phosphate.

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The following quotation from an article by A. Schmierer, in the *Pharmaceutical Journal*, deals with the post-graduate education of German pharmacists.

"In order to provide for the maintenance and extension of the scientific knowledge and practical skill of pharmacists, the German pharmaceutical authorities have established an institution for post-graduate education which arranges for classes and courses of instruction to be held in all parts of Germany. The work is divided between seven main departments and one special department. The main departments are (1) pharmaceutical chemistry, (2) botany and pharmacognosy, (3) applied pharmacy, (4) pharmacology, (5) law, (6) administration, (7) history of pharmacy. The special department includes race and population policy, social policy, health policy, gas and air protection, etc. The instruction may be given in the form of single lectures, series of lectures, evening courses, week-end courses, and full-time courses.

"Every German pharmacist is under an obligation to receive instruction in all the departments to an extent which accords with his circumstances and opportunities of attendance. The obligation is enforceable, but so far no necessity for enforcement has arisen. The cost of instruction is borne partly by the authorities and partly by the individual pharmacist, although in special cases the pharmacist's contribution is remitted. During the first session, which extended over last winter, the demand for instruction was greater than could be fulfilled; 3995 pharmacists participated in the arrangements, approximately 25 per cent of the total number of pharmacists in Germany. The courses are held in the pharmaceutical institutes of universities; in hospital, district, and teaching pharmacies; in technical high schools; and in other schools and laboratories.

"At the conclusion of a course each student is given a certificate and a written summary of the work of the course; he is also given tests to carry out in his pharmacy. Special emphasis is laid on practical work and the use of illustrative material such as films, projections, models, preparations, pictures and experiments. The work in the various departments includes investigation of drugs and medical specialties, simple urine analysis, blood sugar determinations, pregnancy tests, and alcohol in blood tests, microscopical investigations of drugs and drug powders, action of drugs, preparation and testing of apparatus for durability and efficiency, bookkeeping and business administration."