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SUMMARY OF STUDIES ON THE OPTIMAL COMPOSITION OF LOCAL ANESTHETIC SOLUTIONS *

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IT is very difficult, under conditions of practical use, to determine accurately the best composition of a local anesthetic solution. The reason for this is that changes in hydrogen ion concentration, salt balance, the anesthetic constituent, or the vasoconstrictor, may definitely modify the responses to the solution, but only to a relatively small degree. Such solutions are injected in patients who vary tremendously in their sensitivity, and who are usually being subjected to very diverse operative procedures. Under these conditions, the differences in response resulting from variations between patients and between operations may obscure those produced by changes in the local anesthetic solution. Therefore, in order to reveal the effects of modifications of the solutions, it is necessary to inject a large series of patients with the solution in question, comparing it with a parallel series run at the same time in which a standard solution was used as a reference. The data should be statistically analyzed to ensure that apparent differences afford a reliable basis for conclusions. If, in addition, the operations can be standardized so that they are substantially alike, then the differences caused by the solutions, which were obscure before, may stand out in a way which permits their accurate evaluation. Such a study is very necessary, although difficult and tedious to carry out, because only by such means can we determine what modifications of the local anesthetic solution will be beneficial or undesirable, and thus arrive at the optimal composition of such a solution.

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We have had the opportunity, over a seven year period, of carrying on such a series of observations. This opportunity presented itself in the Oral Surgery Clinic of the College of Physicians and Surgeons Dental School, where control of the local anesthetic solutions used was vested in the Department of Pharmacology. We therefore have systematically varied the composition of these solutions, alternating them at short intervals with a fixed solution of simple composition, which was used as a standard of reference. All the information on the responses to these was recorded at the time of injection by a single trained observer delegated to this work. The results have been presented in detail in a series of papers listed in the bibliography below. It is the purpose of the present report to summarize the pertinent results of these studies, so that the information might be available to those who do not have ready access to the journals in which the original articles appeared.

NERVE BLOCK ANESTHESIA

The anesthetic injections to be considered here were all nerve blocks, consisting of mandibular, infraorbital or tuberosity injections in about equal proportions performed for purposes of extractions and related operations. In selecting a local anesthetic solution for injection, the factors to be considered are isotonicity, hydrogen ion concentration, choice of the anesthetic agent, and the vasoconstrictor. These may be discussed in this order.

Isotonicity.—The tissues have an osmotic pressure equivalent to that of 0.9 per cent sodium chloride solution. When a solution of lower osmotic pressure is injected, it causes swelling of the surrounding cells and tissues, and withdraws salt until an equilibrium has been attained. When a hypertonic solution is injected, the extra salt present in the solution diffuses into the tissues, and fluid from the tissues diffuses into the solution, until again an equilibrium has been reached. During this interchange, the tissue cells are either distended or shrunk, the result of which is irritation and more or less permanent damage. Therefore, it is theoretically better to use a solution which has the same osmotic pressure as the tissues.

Procaine hydrochloride, the most commonly used local anesthetic for injection, is isotonic in a concentration of about 4 per cent. Therefore, when procaine is used in any concentration lower than 4 per cent, sodium chloride or some other salt must be added to raise the osmotic pressure. Inasmuch as procaine is ordinarily used in 2 per cent strength, the solutions are made isotonic by addition of 0.45 per cent sodium chloride. Determinations of the freezing points of such solutions, which measure the osmotic pressure indirectly, have shown that these are the correct amounts of procaine and salt for isotonicity.

Use of Potassium Salts.—Some local anesthetic solutions contain about 1.8 per cent of potassium sulfate, instead of the sodium chloride.

Presumably, the potassium salt is used because Kochmann and his associates demonstrated a number of years ago that potassium had a local anesthetic power of its own, when applied under appropriate conditions. In order to test whether the potassium actually potentiated or added to the anesthetic power of procaine, the effects of 2 per cent procaine solution containing 1:50,000 epinephrine made isotonic with either sodium chloride or potassium sulfate were compared in a group of 438 patients (1). The observations were made by the "blind-test" procedure, which consisted of supplying to the oral surgery staff the solutions labeled only with noninformative numbers, both solutions and numbers being changed at short intervals. Each solution was used in routine oral surgical operations and records of the responses were kept by a single trained observer who was not informed as to the composition of the solutions. After all the records were in hand, they were segregated according to the solution used, and the results analyzed statistically. With this procedure there was no opportunity for subjective impressions to bias the results, as may happen with ordinary observational methods. This is extremely important, inasmuch as minor differences may be distorted out of proportion, if the observer has the impression that the new or substitute anesthetic solution is or is not supposed to be a good anesthetic.

The data from this large group of patients indicated that potassium and sodium-containing local anesthetic solutions were practically identical in their anesthetic efficiency. The volumes of solution required, the time and duration of anesthesia, the changes in pulse, blood pressure, and respiration, and the completeness of anesthesia were equal within the limits of expected variation. One objection to the potassium sulfate solutions was that they caused pain at the moment of injection in 26 per cent of the patients as compared to only 17 per cent when the sodium chloride was used. Potassium is more irritating than sodium, so that the increased frequency of painful injections was in keeping with the general actions of this ion. Reactions occurring during the operation, such as perspiration, nervousness, tremors, and faintness, were about alike after the two solutions, as were also the postoperative effects in the injected tissues. These results, therefore, indicated that the use of potassium sulfate, instead of sodium chloride, to make procaine solutions isotonic did not modify in any beneficial way the efficacy of the local anesthetic solution, but caused a small, though objectionable increase in pain during the injection.

Hydrogen Ion Concentration.—Normal tissues have a hydrogen ion concentration of about pH 7.4. When 2 per cent procaine hydrochloride is dissolved in normal salt solution, the pH is between 5.2 and 5.4 or about 100 times the acidity of the tissues. Manufacturers prefer to leave their solutions at this acidity, or higher, since, by so doing, decomposition of the local anesthetic is avoided and the vasoconstrictor ingredient is stabilized. However, the injection of a solution of such

high acidity is theoretically objectionable, since it might damage the tissues. Anesthetic solutions are now available whose acidity has been diminished by the addition of buffer salts, or by combining the procaine with a weaker acid. The practical problem was, therefore, studied as to whether these neutralized solutions actually were clinically better than the ordinary acid solutions.

Procaine Borate.—One of the early attempts to avoid high acidity was to combine procaine with boric acid rather than with hydrochloric acid. Since boric acid is weaker than hydrochloric acid, this resulted in a solution of pH 8.1, or 0.7 pH units more alkaline than the tissues, i.e., more alkaline than was theoretically desired. According to the "blind-test" procedure the responses of 231 patients to 2 per cent procaine hydrochloride and 4 per cent procaine borate were compared (2). Since a 4 per cent procaine borate solution contains as much procaine as a 2 per cent procaine hydrochloride solution, the solutions were tested on the basis of equal concentrations of the procaine molecule. Epinephrine, in a concentration of 1:50,000, was added as a vasoconstrictor. The results showed that the volumes of solutions required, and the speed, duration and completeness of anesthesia, were similar for the two solutions. However, procaine borate caused pain during injection in 10 per cent of the patients as compared to 19 per cent for procaine hydrochloride, indicating that the latter caused irritation on first contact with the tissues almost twice as frequently as did the more neutral solution. Perspiration and nervousness during the course of the anesthesia were about equally frequent after the two solutions, but there was about double the occurrence of tremors and faintness with procaine borate. Since the aim of using procaine borate is to reduce irritation of the tissues, especially important were the tissue reactions in the injected areas, such as muscle spasm, etc. However, the results showed that these were as frequent after procaine borate as after procaine hydrochloride. Apparently, therefore, the alkaline procaine borate solution did not produce any less damage to the tissues than did the acid procaine hydrochloride.

Considerable difficulty was experienced in using procaine borate, since its alkalinity accelerated the decomposition of the epinephrine in the solution. The solution had to be made up fresh just before using, and the epinephrine added immediately before the injection. Inasmuch as these disadvantages were not compensated for by any significant advantage, it seems clear that there is no adequate reason for using procaine borate in preference to procaine hydrochloride.

Buffer Salts.—Since the procaine borate solution was admittedly too alkaline, the irritation caused by this might have been as serious as that from the excess acidity of solutions in current use. Therefore, a solution was tested containing the buffer salts sodium acid phosphate, sodium bicarbonate, and sodium bisulfite, with a pH of 7.4, or exactly that of the tissues. Parallel observations were made on 362 patients as

before, with the "blind-test" procedure, comparing the responses to this neutral buffered solution with those to the usual acid solution. Procaine hydrochloride, 2 per cent in epinephrine 1:50,000, was present in each solution (3).

Comparison of the volumes of the solutions required, speed and duration of anesthesia, effects on blood pressure, pulse and respiratory rates, all showed that the two solutions were substantially alike. Painful injections occurred equally frequently with both, so that adjusting the pH to exactly that of the tissues did not reduce the local irritation on injection to any demonstrable extent. The amount of bleeding, and the reactions occurring during the operations also were quite similar. In the same way, comparison of the after-effects in the tissues during the postoperative period revealed that these were practically identical with the two solutions. At the time of operation, the surgeons reported for each patient as to whether the anesthesia was satisfactory or not. It was satisfactory in 91 per cent of the patients given the acid unbuffered solution as compared to 81.9 per cent of those given the neutralized buffered solution. Therefore, the neutralized buffered solution was no better than the acid solution as judged by the operators and patients. Since again this neutral solution was more difficult to work with than was the acid solution, because of the increased speed of decomposition by the alkalinity, and since these added difficulties in use were not compensated for by any corresponding gain in clinical effectiveness, or in lack of reactions, there appeared to be no reason why such a buffered solution should be preferred to that of the ordinary acid anesthetic solution containing procaine hydrochloride.

Sodium Bisulfite.—About one-half the solutions on the market are not left at the natural pH of 5.4, but are made more acid by the addition of sodium bisulfite in 0.1 to 0.2 per cent strength. This is done to prevent completely the decomposition of the procaine and epinephrine for long periods. The data given above showed that the amount of acidity represented by pH 5.4 was as well tolerated by the tissues as more neutral solutions, but gave no proof that still greater acidity would be tolerated as well. Therefore, it became important to ascertain whether the sodium bisulfite increased the amount of irritation or reactions, in order to determine whether this added acidity was permissible.

Sodium bisulfite is unstable in water and begins to break down almost immediately with the liberation of sulfuric acid and possibly other acid end products. Therefore, solutions of this salt tend to become progressively more acid with time. A solution of chemically pure sodium bisulfite of 0.5 per cent concentration had a pH value of 3.6, when first prepared, but within a month had a pH of 1.7, indicating the production of much free acid (4, 5). When bisulfite was added to local anesthetic solutions of procaine and epinephrine, the same decomposition of the bisulfite with liberation of acid resulted, although the final pH was not shifted as far to the acid side because of the buffer or neu-

tralizing capacity inherent in the procaine and epinephrine. However, such anesthetic solutions became 1.4 pH units more acid in one month, at which time the acid-shift was not yet completed. Accordingly, there was no doubt that the same changes occurred in the anesthetic solutions, although more slowly.

To test whether sodium bisulfite modified the clinical responses to such solutions, a group of 318 patients was operated upon using procaine and epinephrine solutions, one-half of which contained 0.1 per cent sodium bisulfite (5). The same "blind-test" procedure was used as before. The general characteristics of the anesthesia as regards volume used, speed of onset and duration, were the same, so that there was practically no difference between the two solutions in these respects. However, incomplete anesthesia was obtained in 12.7 per cent of the patients injected with the solution without bisulfite, as compared to 20 per cent of incomplete blocks after the bisulfite-containing solution. Therefore, the more highly acid solution was less effective in anesthetizing all the nerve fibers than was that at pH 5.4. The more acid solution did not cause additional pain at the moment of injection, indicating that, if immediate local irritation were produced by this material, the anesthesia prevented the pain from being felt. The injection sites were not any more painful postoperatively after the solution containing sodium bisulfite than after the one without it. However, swelling of the area of injection was definitely increased in frequency by bisulfite solution, since the bisulfite-free solution caused this in only 20 per cent of the patients as compared to 38 per cent when bisulfite was present. In addition, trismus or muscle spasm was more frequent after the bisulfite.

These results showed that sodium bisulfite did not improve the clinical effectiveness of the anesthesia in any important degree. However, it almost doubled the frequency of incomplete anesthesias and increased the amount of postoperative injury to the tissues, both of which were undesirable. Therefore, it was concluded that local anesthetic solutions would be improved if the highly acid bisulfite were omitted, or replaced by some nonirritating agent.

Choice of Local Anesthetic.—A large number of local anesthetics is available for use in the field of general surgery. However, procaine is used to a much greater extent than any other local anesthetic agent, and in general, has proved to be very satisfactory over a period of some forty years. We have investigated two other agents now being actively advocated, namely, monocaine and butyn. Monocaine has a somewhat higher anesthetic efficiency than procaine, as shown by the fact that a 1 per cent solution of monocaine can be used clinically under conditions where 2 per cent procaine is ordinarily employed. It is said to possess a higher systemic toxicity as indicated by fatal doses in animals, so that the greater anesthetic potency might be counter-balanced by greater toxic effects.

Monocaine.—Clinical data were obtained as to whether monocaine was actually any better than procaine as indicated by efficiency of anesthesia, local irritant effects, systemic reactions, and other manifestations of clinical importance. For this purpose, 251 patients were injected with procaine or monocaine, according to the "blind-test" procedure (6). The 2 per cent procaine was found to be about equally as effective as 1 per cent monocaine, as shown by substantially equal volumes of solution being used which produced complete anesthesia with about equal frequency. Monocaine had an apparent advantage in that the anesthesia lasted an average of seventy minutes longer than procaine. This is a difference which might be useful in some fields of surgery, but is not so important in dentistry, where most operations are of relatively brief duration. Monocaine did not have greater effects on pulse rate, blood pressure, or respiration than procaine, so that, if there is a greater toxicity for animals, it is not reflected in the alterations in these functions under conditions of practical use. However, the monocaine solution was more irritating to the tissues at the time of injection, as indicated by 25 per cent of the patients complaining of immediate pain as compared to only 14 per cent after procaine. Reactions during the anesthesia were generally more frequent with monocaine than with procaine; perspiration and tremors occurred about as often with both, but nervousness and fainting reactions were definitely greater after monocaine, indicating a greater degree of systemic disturbance. Inasmuch as these reactions are important from the standpoint of the patient, and give rise to much dread of local anesthesia, it is apparent that monocaine would be less desirable than procaine. In addition, there was evidence of increase in postoperative complications after monocaine over those after procaine. This was indicated by the injection sites being painful postoperatively in one-half the monocaine patients as compared to only one-third of those injected with procaine. There was also an increased amount of inflammatory changes in the operative area in patients given monocaine. This inflammation may not be the direct result of the local anesthetic solution, but, when it occurs more frequently after one solution than after another, the difference can hardly be disregarded.

These observations taken all together indicated that, if the surgeon used monocaine rather than procaine, he would have an anesthesia of longer duration, but such an advantage would be offset by more pain at the time of injection, and more reactions both during the operation and in the postoperative period. Therefore, monocaine really had no great advantages over procaine, but had certain obvious disadvantages which made it undesirable, or at least not the anesthetic of choice, for general use.

Butyn.—Butyn also has a greater toxicity than procaine, both for animals and when used clinically as a local anesthetic in general surgical practice. To determine its comparative value for injections a

group of 231 patients was observed by the "blind-test" procedure as before (7), comparing 0.75 per cent butyn against 2 per cent procaine hydrochloride. The butyn anesthesia was much like that of procaine as to the volumes of solution required and speed of anesthesia. However, the effects of butyn lasted about one hour longer than with procaine. The pulse and respiratory rates and blood pressure changes were the same with the two solutions. Apparently the amounts of butyn administered under conditions of dental practice are too small to produce the greater toxicity of butyn for these functions seen under other conditions. However, butyn suffered from a marked disadvantage in that its injection was painful in 52 per cent of the patients as compared to only 14 per cent when procaine was given. This indicated that butyn was definitely more irritating to the tissues, and that there were apt to be greater local injurious effects from it than from procaine. In addition to this, butyn caused more reactions during the operations than did procaine. For example, perspiration occurred in 30 per cent of the butyn patients as compared to 18 per cent of those given procaine, nervousness in 53 per cent of the butyn patients as compared to 35 per cent of those given procaine, and faintness in 15 per cent of the butyn patients as compared to 6 per cent of those receiving procaine. It seems clear that the patients given butyn were less comfortable during the operations than were those receiving procaine. During the postoperative period, the amount of pain, swelling and other symptoms of inflammatory changes from the anesthetic were substantially alike.

It was concluded that, by the use of butyn, a longer anesthesia was obtained than from procaine but that this longer duration, just as with monocaine, was secured at the expense of more pain at the time of injection and an increased frequency of undesirable reactions during the course of the operation. Therefore, unless there is some special indication for butyn, in place of procaine, there would be very definite disadvantages in its use for injections.

Vasoconstrictors.—The remaining variable factor in the selection of a local anesthetic solution is the vasoconstrictor. Epinephrine has been used so many years that its actions are well understood. However, recently various synthetic substitutes have been advocated with claims of special advantages over epinephrine. Thus it appeared desirable to test the claims as to whether these substitutes are better for local anesthesia than epinephrine. The two compounds especially used for this purpose are cobefrin and neo-synephrine. Both are weaker than epinephrine, and therefore are used in higher concentrations in order to produce adequate vasoconstriction to control the absorption of the local anesthetic, the duration of anesthesia, and the bleeding.

Since the usual concentration of epinephrine is 1:50,000, this was selected as the standard against which the other two agents were compared. In a group of 543 patients, the effects of 1:25,000 epinephrine,

1:10,000 cobefrin and 1:2,500 neo-synephrine were compared with 1:50,000 epinephrine, all the vasoconstrictors being dissolved in 2 per cent procaine hydrochloride with sodium chloride to make the solutions isotonic (8, 9). The results showed that the two epinephrine-containing solutions were about equally effective, since an average of 5.5 cc. of each was required for anesthesia. Cobefrin required 6 cc., and neo-synephrine 6.6 cc. under the same conditions, indicating that definitely larger volumes were necessary for satisfactory anesthesia. The time required for anesthesia to develop ranged from two and eight-tenths minutes for the weak epinephrine to three and three-tenths minutes for neo-synephrine, these differences being practically unimportant. The weaker epinephrine produced anesthesia lasting two and six-tenths hours, which was prolonged one hour by the stronger epinephrine. In comparison, the cobefrin and neo-synephrine solutions gave anesthesias lasting three and one-tenth and two and eight-tenths hours, respectively, both of which were somewhat longer than that of the usual epinephrine.

Since these vasoconstrictors are frequently used for their systemic circulatory actions, the effects on blood pressure and pulse were of considerable interest. Epinephrine, in 1:50,000 concentration, increased the pulse rate an average of 5 beats per minute. The same solution increased the systolic blood pressure but decreased the diastolic pressure, the resulting average increase in pulse pressure being 6.3 mm. of mercury. The solution of 1:25,000 epinephrine produced somewhat greater effects, the pulse increasing 7.5 beats per minute and the pulse pressure being increased 9.2 mm. In contrast, cobefrin produced relatively little change in pulse rate, but the pulse pressure changes were about the same as those with 1:50,000 concentration of epinephrine. On the other hand, neo-synephrine produced a slowing of the pulse (average 3.8 beats per minute), and increased both the systolic and the diastolic pressures but the pulse pressure was increased only an average of 2.1 mm. As a result of the slowing of the pulse and the small increase in pulse pressure, it is probable that the neo-synephrine solution changed the cardiac output little if at all, and definitely less than epinephrine and cobefrin. According to these results it would seem that the neo-synephrine anesthetic solution might produce less cardiovascular strain than epinephrine and cobefrin. The amount of bleeding was diminished by the stronger epinephrine as compared with the weaker epinephrine, as might be expected. However, both cobefrin and neo-synephrine permitted more bleeding than epinephrine solutions, indicating a weaker degree of vasoconstrictor efficiency, with neo-synephrine being somewhat worse than cobefrin. These results indicated that the use of cobefrin or neo-synephrine would result in bloodier operative fields than would epinephrine.

Of great importance to the patient is the frequency of undesirable reactions occurring during the operation. The stronger epinephrine

solution was worse in this respect than the weaker, indicating that these reactions are at least partially produced by the vasoconstrictor drug, since nervousness, tremors, and faintness were more frequent after the 1:25,000 solution of epinephrine than after the 1:50,000 solution. Cobefrin produced about the same amount of perspiration and faintness but more nervousness and tremors than the weaker epinephrine solution. However, the differences were not great enough to establish a real difference between the solutions. It was clear that cobefrin did not cause less reactions than the 1:50,000 epinephrine, in contrast to the claims sometimes made for this substitute. Neo-synephrine caused about the same amount of perspiration, nervousness and tremors as the weaker epinephrine, but less than the 1:25,000 epinephrine. Faintness was only about one-half as frequent after neo-synephrine as after epinephrine and cobefrin. During the postoperative period, the after-effects of the three vasoconstrictors were about the same, this indicating no advantages for the epinephrine substitutes.

These results left no doubt that, when cobefrin or neo-synephrine was substituted for epinephrine in the ordinary solutions of procaine for local anesthesia, a somewhat larger volume of the solution containing an epinephrine substitute would be required than of an epinephrine solution. The neo-synephrine solution would have the advantage of causing less marked changes in the cardiovascular system and also possibly less pronounced side-reactions during the course of the anesthesia, although the differences would be rather small. However, the cobefrin solution would be no different than the usual epinephrine solutions as to cardiovascular effects or reactions during the course of the operations. Therefore, the substitutes would have no claim for precedence according to these criteria. With either cobefrin or neo-synephrine the increased amount of bleeding would constitute an occasional, serious disadvantage, although the importance of this would vary with the type of operation. These results, therefore, have demonstrated that cobefrin was not different from epinephrine, as far as the clinical responses were concerned, but that neo-synephrine might be substituted for epinephrine with advantage in patients where pronounced circulatory effects were to be avoided.

RESUME OF INJECTION SOLUTIONS

It seems clear that there is no great advantage in any of the modifications suggested in the fundamental local anesthetic solution of procaine and epinephrine commonly used, except for special purposes. Two per cent procaine hydrochloride produces anesthesia as well as any of the proposed substitutes. Better anesthesia can probably not be secured, except as to duration, from any available agent. The anesthesia cannot be enhanced usefully by the use of potassium salts instead of sodium chloride to make the solutions isotonic. While it is true that

2 per cent procaine hydrochloride solution, with a pH of 5.4, is more acid than the tissues, this degree of acidity does not cause more irritation to make the solution any less desirable clinically than solutions neutralized to exactly the pH of the tissues. On the other hand, when the pH values are below 5, sufficient irritation is produced to be clinically undesirable. Inasmuch as a certain degree of acidity is desirable for preservation of the local anesthetic and vasoconstrictor agents, there is no good reason for changing the pH of the solution from that of procaine hydrochloride in ordinary salt solutions.

The vasoconstrictor which has been used for years, namely epinephrine, remains the drug of choice for infiltration anesthesia. Cobefrin is merely a weaker form of epinephrine, whose lack of vasoconstrictor power is only partially overcome by using higher concentrations. Even then increased amounts of bleeding are encountered, which may render the operative procedure more difficult. Neo-synephrine may have possible advantages in that it causes somewhat less pronounced circulatory changes than epinephrine and cobefrin. However, here again, the differences are so small as to be of only occasional significance.

TOPICAL ANESTHESIA

Some consideration is desirable of the problem of producing anesthesia of mucous surfaces by local application of various agents. Such topical uses are common in the eye, nasopharynx, urethra and bladder as well as in the oral cavity. Because of the facilities available, topical anesthesia of the oral mucous membranes was studied to determine the most effective agents and their limitations. Such anesthesia is needed for many purposes such as deadening the mucosa before injection, reducing the pain of stomatitis and ulcerative conditions, before scaling operations on the necks of teeth, in curettage of pyorrhoea pockets, for controlling the gagging and nausea in taking radiologic pictures and impressions, etc. Topical anesthesia in the mouth differs from that of other regions in that the surface is made up of a stratified squamous epithelium which has a comparatively low order of sensitivity. Under those conditions, subjective impressions are apt to suggest that anesthesia is present when in fact none exists.

In order to control this factor through the "blind-test" procedure, two topical anesthetic solutions at a time were given surgeons in the Oral Surgery Clinic with the request that one be applied on each side of the mouth on an applicator for two minutes, and the responses be compared and recorded. The solutions were always unidentified as to composition, being labeled with noninformative numbers. In addition, solutions which might be recognized by appearance or smell were disguised by the addition of aromatics and dyes. The solutions were frequently changed, and the same solutions were supplied in different

combinations so that impressions regarding their efficacy would not be carried from one set of observations to another. Frequently blank control solutions consisting of salt solution, or some other non-anesthetic agent, were supplied as one member of the pair. When this was done, they were colored and aromatized in such a way as to be indistinguishable from the true local anesthetic solutions.

Control Solutions.—A total of 933 applications were made of control solutions (10), of which 576 were disguised physiological salt solutions, or Liquor Alkalinus Aromaticus (N.F.). The operators and patients judged that anesthesia resulted from these control solutions 43 per cent of the time. This anesthesia was thought to be complete in 11 per cent, and partial in the remaining 32 per cent. These results indicated that the degree of sensitivity of the oral mucosa was so low that, when a surgeon applied to the mucosa of the mouth an inert solution which he supposed was an anesthetic, both he and the patient believed anesthesia was produced in 43 out of 100 applications.

Since alcohol was sometimes used as the solvent, this was also used as a blank control in the same way as the aqueous solutions. Ten per cent alcohol was tested in 201 patients, with partial or complete anesthesia apparently resulting in 44 per cent, and 95 per cent alcohol in 156 additional patients, with partial anesthesia in 41 per cent and complete in 37 per cent. Thus, 95 per cent alcohol apparently caused some anesthesia in 78 per cent of the patients.

The cause of these positive results with blank solutions obviously was the low sensitivity of the oral mucosa, combined with the subjective factor of expectation of an anesthetic effect. These results indicated that the degree of uncertainty in testing anesthesia in this region was extremely high, and therefore a solution would have to show unusually marked potency before it could be accepted as a true anesthetic.

Ointments.—Two anesthetic ointments, containing 10 per cent acetanilid or benzocaine in petrolatum, were tested. These proved to be ineffective, when applied to the oral mucosa, which is not unexpected inasmuch as this is a mucous surface on which a fatty vehicle could not make effective contact.

Effective Anesthetics.—The other local anesthetic drugs tested included practically all those available for this purpose, namely, tutocaine, metycaine, procaine, cocaine, diothane, butesin, phenol, nupercaine, pantocaine, benzyl alcohol, orthoform, larocaine, butyn, saligenin, menthol, chlorbutanol, and benzocaine. A requirement for local anesthetic efficiency under the conditions of application was that the solution penetrate rapidly, inasmuch as it was not practical to permit more than about a two minute period of application. Therefore, many compounds, which may be effective after prolonged contact, might appear ineffective after this relatively brief application. The concentrations used were those of the commercial solutions exploited for this purpose, or which might be desirable for topical anesthesia.

The most effective compounds were phenol, benzocaine, chlorbutanol, menthol, and saligenin, all of which produced anesthesia in from 97 to 100 per cent of the patients. However, phenol was not generally suitable since it produced a strong caustic action. In the same way, chlorbutanol and menthol were not particularly desirable, since they were irritating in the concentrations required for topical anesthesia.

Benzocaine in Propylene Glycol.—The most effective practical solution tested was 10 per cent benzocaine in 70 per cent alcohol. This caused complete surface anesthesia in 59 per cent of the patients and partial anesthesia in 39 per cent additional, leaving only one person out of 50 who did not experience a high degree of anesthesia from this solution. The benzocaine required 70 per cent alcohol in order to obtain the 10 per cent solution required for effective anesthesia. Alcohol, in this concentration, produces considerable destruction of tissue, and actually resulted in 12 per cent of chemical burns or sloughs at the site of application. Therefore, in spite of the fact that benzocaine was highly effective, it was obviously not desirable for ordinary use.

Since the completion of the previous investigation of topical anesthesia (10) I have demonstrated that 10 per cent or 15 per cent benzocaine in propylene glycol, or in "Carbitol" solvent, is more effective than the alcoholic solution, and is not caustic. Propylene glycol is somewhat superior to "Carbitol" solvent, inasmuch as it is better tolerated by the tissues. This solution has the added merit that it is cheap and stable and without important systemic toxicity. The propylene glycol solution is fairly thick and viscous, and adheres well to the area of application. The best of the commercial solutions was butyn 10 per cent in dilute alcohol. This caused anesthesia in 96 per cent of the patients, so that it ranked very close to the benzocaine solution.

Under the conditions in the mouth, benzocaine would seem to be the topical agent of choice, since it produces a degree of anesthesia which is adequate for most purposes. However, the anesthesia does not extend much below the surface, and therefore, any procedure requiring more than superficial anesthesia would necessitate recourse to injection.

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10. Tainter, M. L.; Throndson, A. H., and Moose, S. M.: Studies in Topical Anesthesia. Further Observations on Efficacy of the More Common Local Anesthetics when used on the Gums and Oral Mucosa, J. Am. Dent. A. 24: 1480–1487 (Sept.) 1937.

MEETING OF THE AMERICAN SOCIETY OF ANESTHETISTS, INC.

MOUNT ROYAL HOTEL, MONTREAL

October 30, 1941—2:00 P.M.

1. Anesthesia for Intrathoracic Operations. (Cinema Illustration.)
   By William B. Neff, M.D., Associate Clinical Professor of Surgery (Anesthesia), Stanford University School of Medicine, San Francisco, Calif.—50 minutes.
   Discussion to be opened by Georges Cousineau, M.D., Montreal, Canada.
2. Acidosis in Anesthesia.
   By M. Digby Leigh, M.D., Anesthetist-in-Chief, Children's Memorial Hospital, Montreal, Canada.—40 minutes.
   Discussion to be opened by D. L. Thomson, M.D., Montreal, Canada.
3. Anesthesia Service for Small Hospitals.
   By Harold R. Griffith, M.M., M.D., C.N., Medical Superintendent, Homeopathic Hospital of Montreal.—40 minutes.
   Discussion to be opened by Sidney Cushing Wiggin, M.D., Boston, Mass.

All members of the American Society of Anesthetists, Inc., and all physicians interested in Anesthesia are urged to attend this meeting.