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The significance of altered ph on the action of the tetracaine / Maurice John Niebaum

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THE SIGNIFICANCE OF ALTERED pH ON THE ACTION OF TETRACAINE

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I. Introduction.

In the field of spinal anesthesia the phenomenon of partial or complete failure occurs. The incidence involves a range of one to five per cent of attempted spinals. Various explanations have been suggested to explain these failures. Maxson (15) classifies partial or complete failures as caused by improper technique or inadequate anesthetic action. Little attention has been given to alteration in spinal fluid pH as a possible cause of anesthetic failure. Since tetracaine has been used extensively for spinal anesthesia, this study attempts to evaluate the significance of altered pH on the action of tetracaine.

II. Historical Account of Spinal Anesthesia.

Studies by early anatomists contributed initial interest in spinal anesthesia when Cotugno (Dominicus Cotumnus) in 1764 discovered the presence of fluid in the brain and spinal cord. Magendie (13) in 1825 studied and eventually described the cerebrospinal circulation.

Pravaz (20)invented the hypodermic syringe in 1851. Alexander Wood(29) in 1853 developed the hollow needle and the glass syringe. Gaedeke(9) in 1855 isolated erythroxylin which Nieman(17) discovered in 1859 and called cocaine. However, anesthetic properties were not discovered until 1862 when Schroff(24) accidentally numbed his tongue with cocaine. Failing to realize the potential use of this phenomenon, it remained for Karl Koller(12) in 1884 to rediscover this phenomenon and introduce cocaine to the field of ophthalmology.

The authentic discovery of spinal anesthesia must be attributed to J. Leonard Corining(4) of New York in 1885. Corning, a neurologist, experimentally injected cocaine into the spine of a dog and produced transient paralysis of the dog's hind legs. Further experimentation led Corning to suggest the name of this phenomenon as spinal anesthesia. Corning contin-

ued to develope the technique of spinal anesthesia, but it was Quincke (21) who described in detail the technique of lumbar puncture. Corning (5) also perfected the technique and apparatus for intradural injection. J. Leonard Corning therefore deserves the recognition as the discoverer of spinal anesthesia.

August Bier (2) of Kiel and Bonn Germany is real father of spinal anesthesia. In 1898, he allowed cocaine to be injected into his own subarachnoid space. Anesthesia was satisfactory, but a post-anesthetic headache was encountered. This led to further injection into the subarachnoid space of an assistant, Schmeiden, without untoward results. Bier's article includes some pertinent observations resulting from his own experience, and it ends by saying that he does not feel justified in continuing his work on humans without carrying out animal experiments with a view to eliminate the untoward side effects. Unlike the enthusiastic sources and reports from American and French authorities, Bier continued to sound a note of caution. By 1904, writing with Donitz (3), he felt justified in stating "after many disappointments we believe now that we can recommend spinal anesthesia," and then he qualified this by adding, "although it is still capable of and needs plenty of improvement."

Tuffier (26) in 1899 extended the use of

spinal anesthesia from the lower extremities onto the genitals and the lower abdomen. Tuffier (28) also worked to improve his own technique by vigorous attention to asepsis. He discussed headache fully and acknowledged an incidence of forty per cent. He also stated that this complication of post-spinal, anesthetic, headache is not serious and that the explanation for it would come later. He was the first to record a follow-up examination of patients operated on under spinal anesthesia. In this series of sixty he found no complications attributable to the anesthetic.

In 1899, the first operations under spinal anesthesia were conducted in the U. S. A. by Tait and Caglieri (26) in San Fransisco. The first published account of an operation under spinal anesthesia was given by Rudolph Matas and Caglieri (14) in 1899. This operation was a hemorrhoidectomy and excellent anesthesia from the waist down was performed with cocaine.

During the early years of the twentieth century witnessed a deluge of trial and reports of spinal anesthesia. Much controversy arose over the dosages and concentrations used because extremely high-level anesthesia was obtained. Explanation for the apparent lack of deaths and untoward results probably lies in the fact that cocaine acts more strongly on the sensory division of the central nervous system

than upon the motor system. Therefore, the popularity of spinal anesthesia declined in the early years of the twentieth century due to technical difficulties and the high mortality encountered. Pitkin's(19) announcements concerning proposed principles of spinal anesthesia did much to preserve the interest and enthusiasm for spinal anesthesia.

Since the use of cocaine produced toxicity and the tendency to cause addiction, the popularity of cocaine in the field of spinal anesthesia declined. Einhorn(8) in 1905 introduced procaine (Novocaine) as a local anesthetic. This drug eliminated the problem of addiction and reduced the danger of serious intoxication. Since that time, a wide variety of anesthetic agents have been developed.

Following Pitkin's announcements a large number of anesthetic agents have been introduced into the field of spinal anesthesia. Tetracaine was introduced into the field of spinal anesthesia in 1930 by Bayers(1) . It is a hydrochloride of para-butylamino benzoyl dimethylamino ethanol, and it also enjoys other trade names now: Amethocaine, Anethaine, Butethanol, Decicaine, Dikaine, Pantocaine, Pontocaine, Regional D. Tetracaine occurs as a white crystalline powder with a melting point of 147°C. It is readily soluble in water or saline and the resulting solution can be

boiled for sterilization. Once prepared it is lethal for non-sporing organisms. One gram dissolves in about seven cubic centimeters of water. It is easily precipitated from solution by bases and carbonates. Anesthetic potency is about ten times that of procaine. Anesthesia occurs within five to ten minutes and lasts for about two hours. The dosages of ten to twenty milligrams are used for spinal anesthesia.

III. Rachiresistance.

In the study of anesthetic failures, two categories have been suggested. Failure to deposit the anesthetic in the subarachnoid space is considered to be the most common cause of failure. The second category involves the phenomenon of inadequate anesthesia. This involves the failure to anesthetize the required operative area. Attempts to explain this phenomenon involve: insufficient dispersion, too low an injection, miscalculation of the proper dose, incorrect posture in relation to specific gravity and individual hyposusceptibility to normal concentrations. Maxson(16) recognized a hyposusceptibility and a hypersusceptibility to the anesthetic drug. Sebrechts(22) recognized these two classes and termed them rachiresistance and rachisensitivity respectively. He termed rachisensitivity to mean those individuals in which the normal dose proves to be excessive or dangerous. He stipulated that those individuals are rachiresistant in which the normal dose is partially or completely ineffective. Sebrechts(23) postulated that rachiresistant individuals share a familial trait for he found five such individuals in the same family. He assumed the anesthetic to be a failure if anesthesia was not complete after fifteen minutes with tetracaine. Shimberg(25) states that in his experience it has taken

forty minutes to achieve anesthesia.

Cullen (7) in 1946 reported that ninety nine percent of spinal anesthetic failures could be ascribed to the failure of administering the anesthetic into the subarachnoid space. He also stated that rare individuals fail to show anesthesia after repeated spinal injections. He postulated that these individuals demonstrate a spinal fluid hydrogen ion concentration such that precipitation of the drug as a base is not effected. Heard (11) in 1938 suggested that the hydrogen ion concentration of spinal fluid may hold the secret of spinal anesthetic failure. Cohen and Knight (6) in 1947 accepted both Cullen's and Heard's challenge but went on to suggest that extreme alkalinity of the spinal fluid was the cause of failure.

Cohen and Knight (6) measured the spinal fluid pH in fifty consecutive spinal anesthetics and found the range to run from 7.35 to 7.9. His reported failures occurred at spinal fluid pH's of 7.8 and 7.91. They suggested that the high alkalinity of the spinal fluid may be an occasional finding inanesthetic failures and may be the cause of failure in certain cases. A Beckman photelectric pH meter was used to measure spinal fluid pH in their experiments.

No mention was made in Cohen's and Knight's report as to the manner in which spinal fluid was

collected. If the collected specimen was excessively exposed to the atmosphere, carbon dioxide equilibration between the spinal fluid and the atmosphere might have distorted the pH values and led to erroneous conclusions.

IV. Spinal Anesthesia and Tetracaine.

All of the important local anesthetics in common clinical use are the salts of primary, secondary or tertiary amines. In solution the anesthetic salt is brought into contact with an alkali and the free anesthetic base is liberated. This separation of the free anesthetic base is one of the most important reactions, for tissue cells and tissue fluids are normally alkaline in reaction. Overton(18) has shown that the free bases of alkaloids are more active pharmacologically than their corresponding salts, and that the free anesthetic bases are four to eight times more potent than their corresponding anesthetic salts. Harris(10) in 1951 stated that when the tissues are abnormally alkaline the separation of free anesthetic base is excessive, and the free base is aggregated into particles sufficiently large to cause their precipitation from solution. He credits this fact to the cause for some spinal failures. He suggested also that aspiration of a highly alkaline spinal fluid into the syringe prior to the intrathecal injection which is cloudy is an indication of a precipitated anesthetic base and that spinal failure would ensue.

Harris (10) also stated that since this separation of free anesthetic base is in the nature of a titration, it follows, when the available alkali has

combined, that no further separation of free base occurs from this cause, and the intrathecal injection of sufficient, additional, local, anesthetic to produce an effective concentration should result in a normal response.

V. Presentation of the Clinical Project.

(a). Procedure.

Spinal fluid was collected from each surgical patient prior to the intrathecal injection of tetracaine for spinal anesthesia. All of these patients received tetracaine mixed with ten per cent glucose in equal volume, thus making them hyperbaric. Each spinal fluid specimen was immediately sealed after collection to avoid contamination and contact with the atmosphere. This procedure was purposely done to avoid bacterial contamination and equilibration with atmospheric carbon dioxide. Bacterial contamination could alter the pH value by releasing acid metabolites, and exposure to atmospheric carbon dioxide and the subsequent equilibration would alter the pH value. After collection in the above manner, the pH value was determined by the Astrup pH radiometer.

Spinal anesthesia onset was measured by determining the length of time required from injection time to achieve adequate, surgical, sensory loss to the level of the zyphoid process. Sensory loss was determined subjectively by loss of pain sensation as elicited with needle pricking. Time values under five minutes were considered normal, and time values of ten or more minutes were considered to be a delay in onset

of spinal anesthesia.

(b). Findings.

This clinical project consisted of fifty-four pH determinations on fifty-four consecutive spinal anesthetics. Spinal anesthesia onset time was measured in each case and recorded. This writer was present at several spinal fluid collections and pH determinations. So, two values were obtained from each patient.

The pH range extended from 7.231 to 7.472, and the mean average pH value was 7.315. These values are presented by graph on the following pages.

Graph number 1 represents the presentation of fifty-four pH determinations in relation to pH increments of 0.20. The abscissa represents pH increments of 0.20 and the ordinate represents the number of spinal fluid pH's falling into the respective increment.

Graph number 2 represents the number of pH values values which demonstrated a delayed onset-time of ten minutes or more. The abscissa represents pH increments of 0.20, and the ordinate represents the number delays in each respective pH increment. In each case the time factor is also tabulated.

(c) Interpretations.

Inspection of graph number 1 reveals the fact

that thisseries of fifty-four pH determinations demonstrates a distribution suggestive of the Bell curve. However, there is a hiatus existing in the pH range of 7.34 to 7.36. To this writer's knowledge this phenomenon has not been reported before. With a larger series, this hiatus most likely would disappear; and the normal Bell curve would be established.

Inspection of graph number 2 reveals five pH determinations which presented a delay in onset of spinal anesthesia. As can be noted, the three longest delays of twenty minutes each, fell considerably to the left of the average mean of 7.315. Therefore, there apparently exists a relationship between higher pH values and delays in the onset of spinal anesthesia. It should be noted also that no delays in onset time occurred in the range of 7.34 to 7.36, the above-mentioned hiatus.

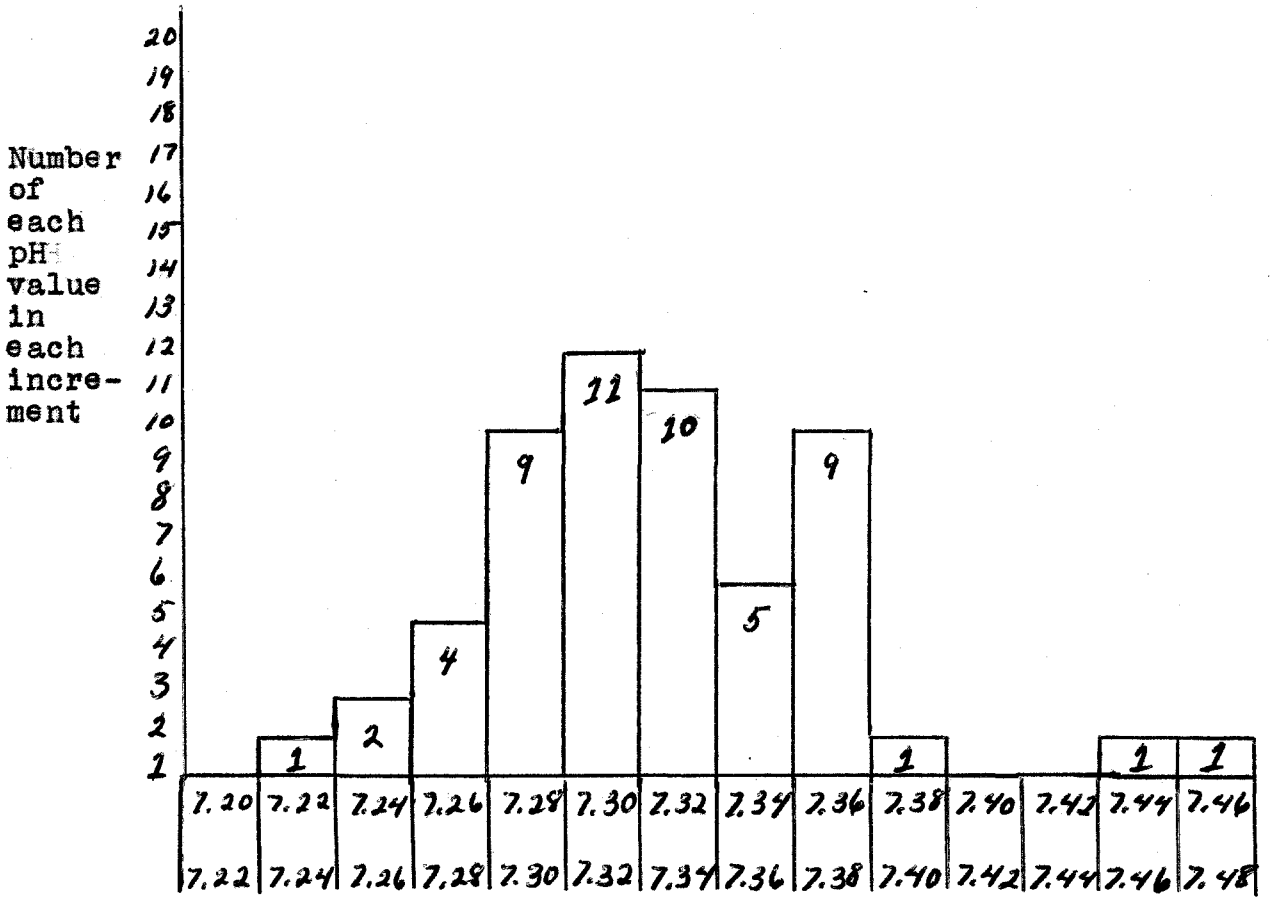
Graph Number 1

Graphical Analysis of Clinical Research into the Relationship between Delayed Onset of Anesthesia and the pH of the Spinal Fluid

Series of 54 pH Determinations

Range 7.231 to 7.472

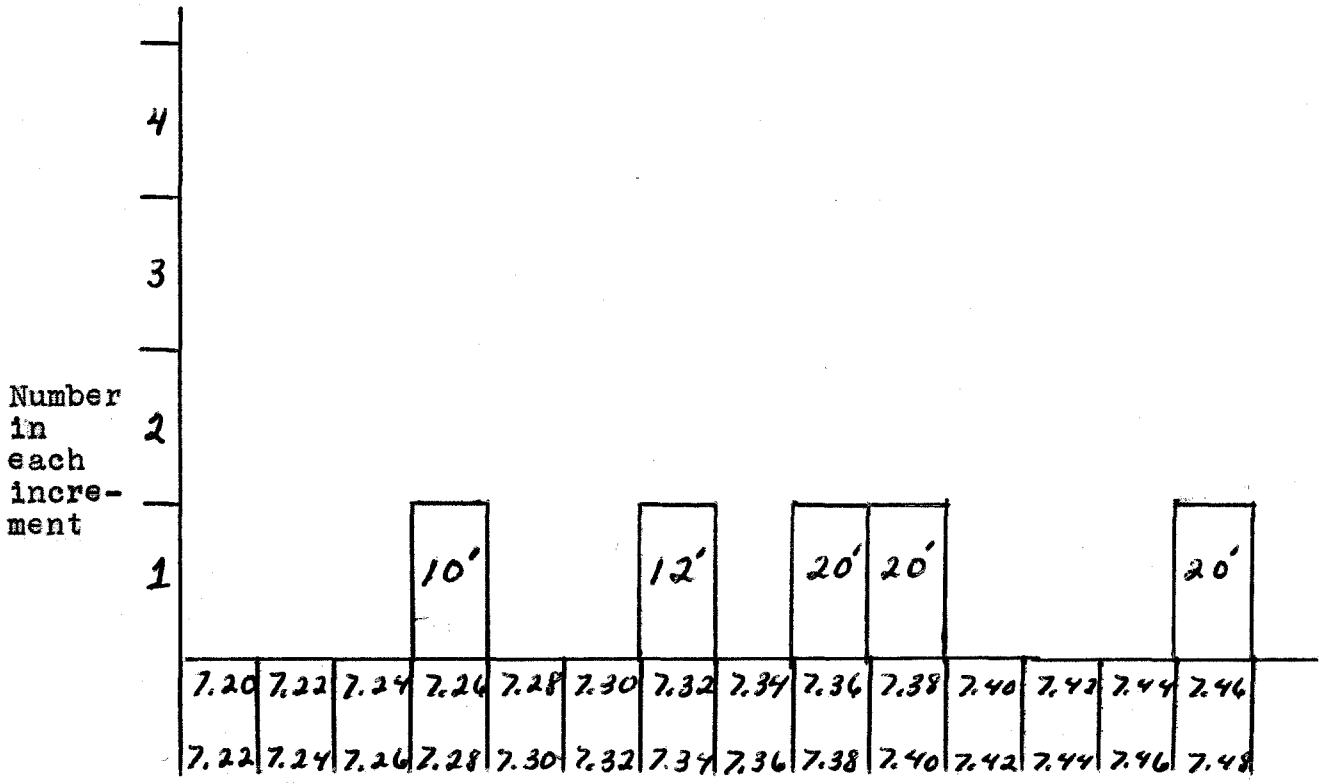
Average 7.315



pH increment of 0.20

Graph Number 2

Graphical analysis and Presentation of the Number of pH Values Representing Delayed Onset times of Ten Minutes or More.



pH increments of 0.20

VI. Practical Considerations.

When this clinical project was initiated, considerations were given to some practical applications in view of this project. If it could be shown that delayed, spinal, anesthesia time could be correlated with either a high or low pH, clinical consideration could be given to adjusting the spinal fluid pH in the operating room to hasten the onset of spinal anesthesia. If the cause of delayed onset was a high pH, the patient could be given five per cent carbon dioxide to lower the pH and therby hasten the onset of anesthesia. If the cause of delayed onset was a low pH, the patient could be asked to hyperventilate and therby blow off carbon dioxide and subsequently raise the pH to a level where anesthetic action would be more rapid. Unfortunately, attempts at these experiments failed to demonstrate results, but these considerations should receive careful sonsiderations when this pH relationship and delayed onset time can be demonstrated. It appears from this project that there doesexist a relationship bewteen a high pH and a delay in anesthesia onset time; so the inhalation of carbon dioxide theoretically should reduce pH and hasten anesthesia onset. This remains to be demonstrated.

VII. Summary.

The history of spinal anesthesia has demonstrated various problems. One of these involves the phenomenon of failure and delayed onset ofanesthesia. Improper technique has be implicated as the causative factor in ninety-five to ninety-nine per cent of failures. The remaining group of failures and delays has been accredited to some failure of action of the anesthetic agent. This study attempted to evaluate the relationship between spinal fluid pH and failure or delay in onset time.

In the series of fifty-four pH determinations correlated with time of onset, five cases demonstrated a delay of ten minutes or more. Of the three that showed a delay of twenty minutes, their respective pH values demonstrated a range above the mean average of 7.315 at 7.362, 7.371, and 7.470. This apparently represents a significant indication that there is a relationship between the higher pH values of the spinal fluid and delays in spinal anesthesia onset. However, this small a series is not conclusive; and a larger series is necessary to implicate the reliability between this hypothetical relationship.

VIII. Conclusions.

The phenomenon of failure in spinal anesthesia is well-known. The majority of these failures can be attributed to improper technique and inexperience, but there remains a group of failures for which there is no explanation asyet. In this clinical project the aspect of spinal fluid pH alteration was investigated as a possible causative factor in spinal anesthesia failures.

The majority of spinal anesthetic agents including tetracaine are acid salts, which when introduced into alkaline body tissuesdissociate to form the free anesthetic base. It has been shown that the anesthetic base is more potent than the anesthetic salt. Consideration isthen given to the degree of acidity or alkalinity of the spinal fluid. It is reasonable to believe that a high or low pH possibly would influence the dissociation of the acid salt and the liberation of the free anesthetic base.

In this clinical project, no failures were found lower than a pH of 7.260. Delayed onset times included those spinals and their pH values which demonstrated an onset time of ten minutes or more. This series demonstrated five delays.at the following pH levels: 7.266, 7.331, 7.362, 7.371, and 7.472. The first value represented a delay in onset of ten minutes,

the second-twelve minutes. The last three demonstrated a delay in onset time of twenty minutes each. These pH values correlated with delays shows a relation between pH levels far above the mean value and delay in onset.

This study does not prove the relationship between high pH and spinal anesthesia failure and delayed onset time, but it does implicate the fact that spinal anesthetic agents seem to exert their physiologic action at a specific pH range and that variation of the spinal fluid pH values into the more alkaline pH range invites failure or delay. It is feasible to hypothesize that the free anesthetic base finds delay in deposition at higher pH levels.

It is obvious that a larger series is yet necessary to prove this relationship. In future studies it would important to have blood pH determinations along withspinal fluid pH to see if their exists a relationship here.

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