

Staff Meeting Bulletin  
Hospitals of the » » »  
University of Minnesota

Histamine Iontophoresis

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Published for the General Staff Meeting each week  
during the school year, October to May, inclusive.

Financed by the Citizens Aid Society.

William A. O'Brien, M.D.

I. LAST WEEKDate: May 17, 1940Place: Recreation Room,  
Powell HallTime: 12:15 to 1:20 P.M.Program: Movie: "Band Concert"Premature Separation of the  
Normally Implanted Placenta  
J. L. McKelvey

Discussion

Present: 156Gertrude Gunn  
Record Librarian

- - -

II. MOVIETitle: "Mother Goose Goes Hollywood"

A Walt Disney Short

Released by: R-K-0

- - -

III. ANNOUNCEMENTSUNIVERSITY OF MINNESOTA PRESS  
Announces the following  
medical books:

1. Physicians of the Mayo Clinic  
(Biography and bibliography) \$10.00
2. A Manual of Operating Room  
Procedures -  
A. W. Hoppe and L. Halverson 2.00

3. Iodine and the Incidence of  
Goiter  
J. F. McClendon \$5.00
4. The Growth of the Surface Area  
of the Human Body  
Edith Boyd 5.00
5. Development and Growth of the  
External Dimensions of the  
Human Body in the Fetal Period  
R. E. Scammon and L. A.  
Calkins 5.00
6. Chemistry and Medicine  
Edited by Maurice B. Visscher 4.50
7. Let's Talk About Your Baby  
H. Kent Tenney, Jr. 1.00
8. The Kosher Code of the  
Orthodox Jew  
S. J. Levin and E. A. Boyden 4.50
9. Child Care and Training  
(fifth edition)  
M. L. Faegre and John E.  
Anderson 2.50
10. The History of the Mayo Clinic  
January, 1940.

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#### IV. HISTAMINE IONTOPHORESIS

##### A Report of Forty Cases

R. E. Reiley

Histamine iontophoresis was introduced by Deutsch<sup>1</sup> in 1931 as an efficient method of producing arteriolar and capillary dilatation of the smaller vessels together with increased permeability of the vessel walls. There is increased blood supply to the affected tissues, therefore increase in nutrition, metabolism, and temperature, Augmentation of blood supply is and has been commonly accomplished by use of indirect hyperemia using diathermy, counter-irritants, hot-water bottles and forms of infra-red radiation. Nerve section and ganglionectomy have been performed in certain severe cases of rheumatoid arthritis.

##### Pharmacology of Histamine<sup>2</sup>

Histamine or Ergamine acid phosphate is found in all tissue extracts and is present in large amounts in the normal stool. It is a cleavage product of proteins produced by acids, ferments, or bacteria. It is rapidly destroyed by bacteria, therefore not effective when given by mouth. Subcutaneous or intravenous injections of histamine produce powerful effects on the circulation and smooth muscles. Bronchioles and larger arteries are constricted, arterioles and capillaries are dilated.

Quantities of more than 1 mg. when injected may cause alarming symptoms consisting of headache, vomiting, fall in blood pressure, and respiratory disturbances.

Kling<sup>4</sup> demonstrated the powerful influence of histamine on the peripheral circulation by putting a drop of a 1:1,000 solution of histamine on the skin, then pricking the skin with a sharp needle. Within 5 minutes an urticarial wheal surrounded by a red flare developed. This demonstrated a triple reaction:  
"1. Local dilatation and increase in blood flow in the minute vessels (purple

spot); 2. A local increase in the permeability of the capillaries, producing a wheal; and 3. A widespread dilation of the surrounding arterioles (flare)."

The above effects can be obtained by any method carrying the drug to the arterioles and capillaries such as injection, application of ointments or solutions and pricking the skin. Scratches and needle pricks, however, produce bruises preventing frequent re-application, therefore, application of histamine by iontophoresis is a more satisfactory method. It is simple, harmless and can be accurately controlled.

For application of histamine by iontophoresis a source of smooth galvanic current is used having an accurate milliammeter reading to 50 M.A. Histamine is an alkaloid therefore carries the electrical charge toward the negative pole as it is an anion. The solution is for this reason applied at the positive or active pole which consists of filter paper soaked in a solution of 1:3,000 strength and corresponding to the size of the area being treated. Over this is wrapped ordinary sheet wadding soaked in normal saline to prevent evaporation of the solution and hold the filter paper in place by a rubber Davol bandage. The negative or dispersive electrode consists of a padded lead plate placed on the chest, back, or abdomen as occasion arises.

Kling<sup>4</sup> used a non-metal basin filled with physiologic salt solution in which an insulated metal plate was placed. One hand was immersed in the solution.

Following application of the electrode the current is turned on and gradually increased to a strength of  $\frac{1}{4}$  to  $\frac{1}{2}$  M.A. per square inch for 5 minutes. If a galvanic apparatus is not available the scratch method may be used. A piece of gauze soaked in the solution is rubbed into scratches over the involved area.

##### Subjective Sensations

As the current is turned on the patient notices a sensation of prickling as if they are being pricked with needles. The

current is slowly increased to maximum and the prickling sensation is replaced by an itching sensation. When the current is turned off slowly the prickling sensation returns. As soon as the positive or active electrode is removed the patient will complain of itching for 10 to 30 minutes.

### Objective Observations

During treatment the skin becomes reddened and a flare appears around the treated area. On removal of the active electrode wheals appear in the red flare and may blend into one large patch of urticaria if iontophoresis is used. The skin temperature of the treated part rises 3 to 6 degrees F. The wheals or urticaria usually disappear in from 10 - 30 minutes leaving the reddened skin which returns to its normal appearance in from 3 - 6 hours.

Studies by Bettmann<sup>9</sup> showed a marked increase in number of capillaries visualized, marked increase in circulation rate and dilation of sub-papillary vessels. Bettmann demonstrated experimentally that iontophoresis of a 10% solution of sodium iodide preceded by an application of histamine showed, in sections, particles of iodine precipitated in all layers of the skin; whereas, when not preceded by a histamine application the particles were precipitated only in the superficial layers by thallium acetate.

These experiments serve to show that the action of the galvanic current is to carry histamine to the capillaries and arterioles in the corium. So far it is the most satisfactory carrier for this purpose. Controversy over how deep drugs can be carried into tissues by this method does not affect the use of histamine.

Acetyl-beta-Methylcholine or Mecholyl has also been used extensively by this method but the majority of observers have found it less satisfactory as it requires a higher concentration of solution, longer period of application, larger concentration of current, and systemic reactions are more frequent and alarming. Its most recent application is an ointment of analgesic balm applied to the part

together with infra-red radiation reported by Cohen and Rosen.<sup>8</sup>

The term "Ionization" is applied to the dissociation of a salt into its ions. Electrical current does not accomplish this, it merely demonstrates the dissociation. The movement exhibited by a charged colloid in an electric field is termed electrophoretic or cataphoretic mobility.

Electroosmosis should be the term of choice when a substance is carried passively with the electroosmotic flow of liquid, e.g., alcohol or procaine base. Iontophoresis is the term used when the therapeutic mechanism is believed due to independent ionic migration. Abramson and Alley<sup>3</sup> have reported and clarified the mechanism of histamine iontophoresis from an aqueous media. It is not the premise of this paper to discuss the advantages and disadvantages of methods nor the technical aspects of electro-kinetic phenomena. Therefore, with the preceding brief comments on technique and fundamentals the rationale of this particular type of therapy is a question worthy of consideration.

Histamine iontophoresis has found its largest application in rheumatic conditions. Abnormal peripheral circulation, consisting of cyanotic, cold, clammy hands and feet, is frequent and common in most types and stages of these conditions. Vasoc constriction producing ischemia is responsible for painful contractions characterizing various forms of muscular rheumatism as torticollis, lumbago, myalgia of the shoulder and ilio-tibial bands. Circulatory disturbances as vasospasm or inflammation are important factors in production of soft tissue changes in arthritis, peri-articular swelling, contracture and atrophy of tendons and muscles, induration of joint capsules and trophic skin changes.

Whether bony changes occur as a result of abnormal circulation in the joints or not is controversial. However, it is significant that changes occur in the ends of the long bones and that overgrowth of the patella in dogs has been produced by ligature of soft tissues.

Abnormalities in blood flow, carbon dioxide content, and capillaries of arthritic patients have also been demonstrated.

Many workers have, however, noted the absence of arthritic changes in extremities amputated for diabetic or arteriosclerotic gangrene, thus casting doubt on the primary importance of circulatory disturbances. Painful muscle conditions are present however, before any joint or bony changes are apparent as a rule. Regardless of whether circulatory changes are primary or secondary factors in the etiology of arthritis, disturbances of the peripheral circulation and their correction are one of the main objectives of the therapy of rheumatic conditions. It is on this principle that the use of histamine has found its basis.

Many series of cases have been reported, however Kling et al have probably accumulated the largest series yet reported. He has been working since 1932 and in 1933 reported 730 cases of rheumatic affections with 83.5% cured or improved, 16.5% not benefited, and temporary relief in 24.8%. In 1935 Kling<sup>4</sup> reported 150 cases with cure or improvement in 74.6%. This same worker reported 259 cases in 1939 with cure or improvement in 73.3%. The above

series of cases included vasospastic conditions, Buerger's disease, myositis, sub-acromial bursitis, teno-synovitis brachial neuralgia, post-traumatic arthritis, rheumatoid arthritis, gout, G.C. arthritis, osteoarthritis, sacro-iliac arthritis, spondylarthritis and radiculitis. Of the various joint conditions best results were in post-traumatic arthritis, and least in sacro-iliac arthritis. Soft tissue affections as myositis, sub-acromial bursitis, teno-synovitis, and brachial neuralgia showed cure or improvement in over 90% of acute cases. In rheumatoid arthritis, no effect was noted on articular effusions. Kling concluded that therapy in arthritis is more effective on the smaller than the larger joints.

Because of the prevalence of rheumatoid disease in this section of the country and, more especially, the large number of cases being treated at the University Hospital, it seemed advisable to undertake this therapy in the light of the encouraging results published. The cases selected for this study were from the Medical Out-Patient Department with their permission and cooperation.

<u>Number Cases</u>	<u>Complete Relief</u>	<u>Partial Relief</u>	<u>No Relief</u>
40	23 57.5%	12 30%	5 12.5%

<u>Patients who received vaccine</u>	<u>Other Rx total</u>	<u>Histamine only</u>
30	33	7

Duration of Symptoms

1 day -- 18 years

Average

4.43 years

Symptoms 2 years or less

No. 16    Relief 16    100%

2 years or more

No. 24    Relief 24    79.1%

Type of Cases

Arthritis	31 cases	1 old G.C.	26 relieved
Brachial neuralgia	2 cases		all relieved
Back Strain	1 case		all relieved
Back Sprain	3 cases		all relieved
Buerger's disease	1 case		partial
Myalgia	2 cases		all relieved

Arthritics not relieved

1.	3 years	Cervical arthritis	x-ray, vaccine, Bee Venom, Histamine Injection
2.	3 years	Generalized	Vaccine, diathermy
3.	7 years	Knees	Diathermy, vaccine, chaulmoogra oil
4.	11 years	Sacro-iliac	Vaccine, diathermy
5.	6 years	Shoulders	Vaccine, Bee Venom, diathermy

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Treatments were given according to the severity of the case, daily, and 3x weekly. A 1:3,000 solution of histamine dihydrochloride was applied to the affected part or parts on filter paper, sheet wadding soaked in normal saline was then applied over this, then a metal strip electrode held in place by a rubber Davol bandage was put on. As the indifferent electrode a padded metal plate was used, a standard time of 5 minutes was used and the current intensity varied according to the size of the area and patient's tolerance. In most cases a series of 12 treatments was given as a therapeutic trial. A control series of 10 cases was run using normal saline on both poles, and a series of 10 cases using histamine on the active pole with no current. On the former control series a reflex vaso-dilation occurred which rapidly disappeared with no flare or wheal formation. On the latter there was no reaction. In both series no therapeutic effect was observed. All cases treated were

ambulatory and treated in the Out-Patient Department.

The cases selected for treatment all had received other types of therapy including vaccine, diathermy, bee-venom, chaulmoogra oil, supports, and fever therapy. It was felt that an adequate test was to take cases which had not responded to these types of therapy. Results were evaluated according to the symptomatic relief. It would be presumptuous to assume, in arthritics, that a cure was obtained without adequate follow-ups of the cases under treatment.

In the series of 40 cases, 31 were arthritics of various types and manifestations, 2 cases of brachial neuralgia, 1 case of back strain, 3 cases of back sprain, 1 case of Buerger's disease, and 2 cases of myalgia.

The study covered a period from Aug. 1, 1939 to February 1940.

In the table shown are listed results as tabulated. Follow-ups have been obtained on most of these cases, however it is obvious that over such a short period of time it is difficult to evaluate results in a disease as arthritis characterized by spontaneous remissions and exacerbations, and wishful thinking on the part of chronically affected patients. However, results in this series compare favorably with those of other workers, therefore, it may be assumed that they are reasonably accurate. It is of interest to note the average duration of symptoms, also that the cases which received no relief had a duration of 3 years or more and had received no complete relief from other types of therapy.

Also of interest was case having the longest history, a 76 year old white male having low back pain with stiffness for 20 years who received complete relief from the first treatment. This patient's x-ray showed arthritis of the sacro-iliac joints and the lower lumbar spine. For the past two years he has been unable to bend over and tie his shoe-laces, together with difficulty in starting the urinary stream, and frequency. He was given a series of 12 treatments with relief of all symptoms. He was discharged and 6 weeks later contracted an upper respiratory infection with an exacerbation of symptoms. He returned for another series of treatments and again was relieved. To date he has had no exacerbation.

Where other types of therapy were indicated, these were instituted, e.g., arch supports and back supports, following the course of treatments.

As other observers have noted in joint involvement, the more readily accessible joints, especially fingers, feet, back, and wrists, responded better to treatment. Knees and shoulders show the least favorable results. Those joints showing bony destruction in x-rays also do not respond favorably. Martin and Eaton<sup>7</sup>, using mecholy, reported no beneficial effects on 3 cases of spondylarthritis of Marie-Strümpell type.

An important feature of histamine iontophoresis is that if the patient is

to receive any relief from the treatments it is usually noted that the first one to three will give partial or complete relief. To test this feature those patients who received no relief were given a standard series of treatments and a few as many as twenty-four with no relief.

Histamine will not prevent exacerbations in other locations. Toxic reactions are few; in nearly 500 treatments only one case had an immediate or allergic reaction. This consisted of generalized flushing, rapid respirations, dilated pupils, dizziness, and fall in blood-pressure. This was immediately controlled by a subcutaneous injection of adrenalin. One other patient experienced some difficulty breathing 4 hours after treatment. This was obviated by giving the patient a 3/8 grain capsule of ephedrine sulfate at the end of the treatment.

Boyd, Osborne, and Markson<sup>10</sup>, using mecholy reported that most of their cases (35) had a sense of heaviness on the chest and inspired deeper, also flushed face, neck, and ears, and marked perspiration. In the average treatment these symptoms do not appear using histamine; however, one should be prepared to meet them.

In view of this series and those of others, it may be said that histamine iontophoresis offers a simple, harmless adjunct to arthritic therapy and shows a high degree of symptomatic relief in this and other conditions manifesting peripheral vascular abnormalities. It is economical from the patient's standpoint and does not require expensive equipment. The source of galvanic current may be obtained from batteries or household current. Treatments may be carried out in the home.

This method of introducing drugs into the body has been applied effectively also to zinc solution, copper solutions, silver nitrate, adrenalin, insulin, magnesium sulfate, and more recently to desensitizing patients afflicted with allergy. Harpuder<sup>6</sup> has used nupercaine by iontophoresis for blocking referred pain.



Other conditions said to be benefited by drug iontophoresis are trachoma, chronic otorrhea, hay fever and various forms of rhinitis, indolent ulcers, scars, and cervicitis.

### Summary

1. A series of 40 cases treated by histamine iontophoresis are reported with high symptomatic relief.
2. The method used is simple and harmless if properly done.
3. Histamine iontophoresis is not held as a "cure" but a valuable adjunct to arthritic therapy.
4. It will definitely benefit certain types of specified muscle conditions as gout, myalgias, strain, and sprain.
5. It has a definite place in treatment of peripheral vascular disorders as acroparaesthesia and Reynaud's disease.
6. Deutsch is credited with introducing this method of introducing vasodilating drugs; however the extensive work by Kling, et al has served to popularize it in this country and inspire its use.
7. Introduction of drugs into body tissues by this method has a wide application and opens new fields of therapy.
8. It does not require expensive equipment and is economical to the patient.

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V. GOSSIP

Off we go for Watertown to attend the annual meeting of the South Dakota State Medical Association. The day is warm and windy. The new car pleases as the wonders of "overdrive" unfold themselves. At Norwood they are having one of these whisker celebrations to commemorate something or other. About this time we pick up the Milwaukee's Olympian as a traveling companion on the adjacent track. The engine seems to express the mood of a transcontinental train as it snarls through the small towns accompanied by wild ringing of the bell and enormous clouds of dust. The train stops at Olivia but it soon joins me as we continue on our way. The assorted cars seem out of place compared with a streamliner's smart appearance. The old yellow paint is getting pretty thin in spots. At Sacred Heart I recall that this town has only one Irish family. We now reach the Minnesota Valley at Granite Falls. From a high point, the rocks in the distance and the stream below are a decided contrast to the flat plains behind. Just below the edge of the cliff is the tuberculosis sanitorium directed by our good friends - the Jordans. Up the valley we go to Montevideo. Now we pass the golf course where George's Pattie Bergh "to be" will some day amuse herself playing a course which today is mostly dandelions. I imagine that finding a golf ball in that mess would be quite a problem. The trees have been in bloom all the way. Children in small towns are everywhere at play. The women lounge around their yards idly inspecting imaginary flaws in their homes but in reality enjoying the sunshine, I suppose. At Montevideo in the restaurant someone comes to the defense of the Germans - says they have always been good neighbors, etc. I didn't stay for the finish. Now we are passing Dawson, Minnesota, and on my left is the cemetery where Herman Johnson, who did such good work in the interests of better medical legislation in Minnesota, lies buried. Before long the tell-tale plains of Dakota which really start on the Minnesota side are evident. Seagulls follow the farmers in the fields as the ground is being worked. Now the houses are farther apart and eventually Watertown is reached. The medical meeting is held at the local hotel with approx-

imately one-third of the state membership present. O. S. Randall is at the door to meet us. There are also several other Minnesota graduates, including Alonzo Peake, and Michigan-graduate State Association Secretary, Sherwood, of Madison. The meeting seems small, although this is said to be about the regular size. Inside the meeting room a lecturer is telling what they are doing up at the State Hospital with insulin and metrazol treatments. A very interesting set of figures are released showing that the county is being saved money by sending patients home but not the institution, which is rather difficult for me to understand. I learned, however, that in the last two years 165 mental patients have been returned after these special treatments. My turn comes for "Health Problems Incident to Advancing Years," and the South Dakota profession seems interested, as there have been very few replacements in the group. The average physician's age is higher than in most states. In addition, the span of life in South Dakota is greater than any other state in the Union -- one of these tragedies so far as the place it had to happen is concerned. Next we go to a lake. Of all things in South Dakota and a large lake at that. With South Dakota's wind added to the water it creates quite a nautical effect. In our host's home, a negro boy from Oklahoma serves refreshments in a grand manner. I learn that he is an ex-private of one of the colored regiments down on the border and that he was there in the "revolution of 1929." We talked "border" because that is also home to me. I am not prepared for this - a boat which came through from the seacoast largely on its own, and, of all things, with red sails. A boat with "Red Sails in the Sunset" on a lashing lake in South Dakota. Then to dinner where Urologist William Braasch discourses on the National Physician's Committee and my turn comes on "Recent Advances in Medicine." After that there was much gaiety at Brown's home where came many of the elite ala Morris. Eventually, the hour for parting arrives. The moon is shining, and as I roll along the prairie, here before me is an enormous building called Prairie Moon Dance Hall. The miles roll behind; few cars are seen. Coffee stops where most discussion is about fishing shorten the trip.....