The Failure of Histidine and Vitamin C, and of Ether, to Improve the Peripheral Circulation

Report of Studies on Subjects with Normal Arterial Circulation and with Occlusive Arterial Diseases

By Sydney J. Weisman, M.D., and Edgar V. Allen, M.D.

Clinical experience has not confirmed previous observations that intravenous injection of vitamin C and intramuscular injection of histidine monohydrochloride are useful in the treatment of peripheral ischemia observed in arteriosclerosis obliterans. Clinical experience with intravenous injection of ether has failed to indicate that this method of treatment is of value in improving the peripheral arterial circulation in thrombo-angitis obliterans and arteriosclerosis obliterans.

Recent studies have indicated that the peripheral arterial circulation of patients with ischemia due to arterial occlusion can be improved as a result of the use of histidine and vitamin C, and as a result of intravenous injection of ether. Because cerebral ischemia so frequently is resistant to treatment, we have carried out studies to evaluate, critically, these two methods of treatment. In all instances the diagnoses were made by experienced observers.

Treatment with Histidine and Vitamin C

Series A. In 5 cases, arteriosclerosis obliterans was treated with an initial intravenous injection of 500 mg. of vitamin C, followed by subcutaneous injections of 200 mg. of vitamin C and intramuscular injections of 5 cc. of a 4 per cent aqueous solution of histidine monohydrochloride three days daily.

Case 1.—A man, 63 years of age, was admitted to the hospital because of ischemia of the lower extremities and diabetes. Sudden arterial occlusion of the left popliteal artery had occurred two days previously. The left foot was markedly ischemic and very painful. Three days of treatment failed to relieve pain; signs of ischemia were progressive and amputation was necessary.

Case 2.—A man, 61 years of age, was admitted to the hospital because of arteriosclerosis obliterans; infarction of the right second toe had occurred two weeks previously. Improvement occurred during the first three days in the hospital. At the end of that time the use of histidine and vitamin C was added to the therapeutic program and continued for five days. Healing occurred.

Case 3.—A man, 69 years of age, was admitted to the hospital because of arteriosclerosis obliterans associated with infarcted areas on the right second, third and fifth toes and other signs of marked ischemia. Treatment was carried out for fifteen days but pain and necrosis became increasingly more marked; amputation of the leg was necessary.

Case 4.—A man, 65 years of age, was admitted to the hospital because of arteriosclerosis obliterans associated with marked cyanosis of the right first toe which was moderately painful. Treatment for four days did not produce any change in the objective and subjective evidence of ischemia. The patient left the hospital and returned to his home where amputation was performed subsequently.

Case 5.—A man, 54 years of age, was admitted to the hospital because of arteriosclerosis obliterans, diabetes mellitus, alcoholism and narcotic addiction. There was a deep ulcer measuring 2 cm. in diameter over the right heel, which was extremely painful. Treatment with histidine and vitamin C was carried out for four days without benefit. Other treatment was carried out for an additional two months without benefit. The patient returned to his home but was readmitted to the hospital two months later. The right heel was necrotic and amputation of the leg was necessary.

Summary of Cases Reported in Series A: Observation of the cases reported in this series proves nothing except that very short courses
of treatment with histidine and vitamin C are wholly ineffective in relieving the pain and other manifestations of ischemia in arteriosclerosis obliterans.

**Series B.** The patients in this series were treated according to the following schedule. An initial intravenous injection of 500 mg. of vitamin C was given and 200 mg. of vitamin C was given orally three times daily. Histidine monohydrochloride in amounts of 5 ec. of a 4 per cent aqueous solution was injected intramuscularly and 100 mg. of vitamin C were injected subcutaneously every four hours during the entire night and day.

**Case 6.**—A man, 54 years of age, was admitted to the hospital because of diabetes mellitus and arteriosclerosis obliterans. There were ischemic ulcers on the lateral surface of the proximal phalanx of the left fourth toe and on the opposing surface of the left fifth toe, associated with moderate pain. Treatment was carried out for thirty-seven days. There was no change in the appearance of the ulcers and no relief of pain.

**Case 7.**—A woman, 77 years of age, was admitted to the hospital because of arteriosclerosis obliterans and diabetes mellitus. Amputation of the right leg had been performed four years previously because of gangrene. Pain had begun in the left first toe two months previously and gangrene of the toe had been present for one week. Treatment with histidine and vitamin C was carried out for thirty-eight days; pain increased in severity and necrosis remained unchanged. Amputation of the leg was necessary.

**Case 8.**—A man, 58 years of age, was admitted to the hospital because of arteriosclerosis obliterans associated with diabetes mellitus. A fracture of the right tibia thirty-five years previously had resulted in adhesion of the skin to the site of the fracture. Massage of this area three months before admission had resulted in a reddened painful area which had been excised. Healing did not occur. On examination, there was, in addition to arterial occlusion and other signs of ischemia, a necrotic ulcer over the midportion of the right tibia. The area was debrided five days after admission to the hospital; a denuded area remained over the tibia which measured 5.5 by 3.6 cm. Treatment with histidine and vitamin C was carried out for thirty-eight days; there was very minor improvement in the appearance of the lesion. The patient returned to his home.

**Case 9.**—A man, 78 years of age, was admitted to the hospital because of arteriosclerosis obliterans. There was an area of necrosis measuring 2 by 2 cm. over the lateral surface of the distal end of the left fifth metatarsal bone, which was surrounded by an area of inflammation. Pain was mild and was controlled with acetylsalicylic acid and whiskey. The cellulitis disappeared as a result of treatment with penicillin. Treatment with histidine and vitamin C was carried out for nineteen days. Pain became intense and intractable, the gangrenous area progressed in size, and amputation of the leg was necessary.

**Case 10.**—A man, 60 years of age, was admitted to the hospital because of arteriosclerosis obliterans associated with pain in the left foot (ischemic neuritis) and particularly in the left second toe, on which there had been an ischemic ulcer for six weeks. Pain subsided rapidly and was present in a very minor degree when treatment with histidine and vitamin C was added to the usual program of treatment on the eighth hospital day. It was continued for twenty-nine days. The second toe was amputated near the end of this time because the necrotic lesion extended into the distal interphalangeal joint; healing occurred slowly but was complete.

**Summary of Observations of Cases Reported in Series B:** It is quite apparent that histidine and vitamin C were valueless in the treatment in the first 4 cases reported in this series. Whether or not they contributed to the good results in the fifth case is a question which cannot be answered. We have repeatedly observed equally good results in instances in which histidine and vitamin C have not been used. Determinations were made of the temperature of the skin of the toes, under basal conditions before and after the courses of treatment. Changes were minor and not indicative of improved circulation as a result of treatment.

**Series C.** A study was made of the effect on peripheral circulation, as determined by studies of temperatures of skin, of single injections of vitamin C and histidine. Four patients had arteriosclerosis obliterans and 4 patients had normal peripheral arterial circulation. All patients had abstained from the use of food, alcohol, drugs, and tobacco for several hours previously and were at rest in a "constant" environmental temperature which varied a maximum of 0.4 degrees C. during each study period. In all instances but two the environmental temperature was between 25.0 and 26.0 C.; in two instances it was between 24.0 and 25.0 C. The foregoing are considered basal conditions and will be so designated subsequently in this presentation.

Each patient was given 500 mg. of vitamin
C intravenously and rested until the temperature of the skin of the digits had become stabilized. An intramuscular injection of 5 cc. of 4 per cent aqueous solution of histidine monohydrochloride and a subcutaneous injection of 100 mg. of vitamin C were then given and the temperature of the skin was determined at intervals of ten minutes over periods varying from forty minutes to three and a half hours. The original temperature of the skin of the toes in the different studies varied from 24.0 to 29.0 C.; these temperatures easily permit demonstration of arteriolar dilatation. The original temperatures of the skin of the fingers in the different studies varied from 30.0 to 36.0 C. In no instance could it be determined that the injection of histidine causes an increase in blood flow to the digits. Indeed, in a number of instances, the temperature of the skin decreased after injections, and one might conclude, incautiously, that the injection of histidine caused a decrease in the peripheral circulation. Actually the variations in skin temperature were wholly nonspecific and might as well have followed the intramuscular injection of water as of histidine.

**TREATMENT WITH THE INTRAVENOUS INJECTION OF ETHER**

**Series E.** Diethyl ether was administered as recommended by Katz, except that 25 cc. of ether were added to 500 cc. of an isotonic solution of sodium chloride instead of being added to 1,000 cc. of that solution. The solution of sodium chloride was cooled in the refrigerator for at least twelve hours, and the ether was added immediately before beginning the injection, which occupied approximately one hour. All patients complained of marked burning along the course of the vein during the first few minutes of the injection. Because of local and systemic discomfort, none of the patients permitted twenty-four daily injections, as recommended by Katz.

**Case 6.**—The patient had been treated previously in Series B. Ether was injected daily for nine days, during the first six of which the patient noted relief of pain for periods varying from five to fifteen hours. During the last three days he did not note relief from the injection and on the ninth day of injection he commented that the pain was the worst it had been since he had been in the hospital. The appearance of the ulcer remained unchanged. Amputation of the leg was necessary.

**Case 11.**—A man, 42 years of age, was admitted to the hospital because of thromboangitis obliterans. Amputation of the right leg below the knee had been performed four years previously and there had been recurrent superficial phlebitis of the left leg and infarction of the left second toe for three months prior to admission. Marked ischemia of the left foot was evident and there was early gangrene of the left second toe associated with severe pain. Ether was injected on three successive days without relief of pain. Lumbar sympathectomy was then performed and was followed by gradual relief of pain; restoration of circulation to the toe occurred gradually.

**Case 12.**—A man, 45 years of age, was admitted to the hospital because of arteriosclerosis obliterans. Ischemic neuritis, characterized by severe burning pain, had affected the right foot for four months. An ischemic ulcer had been present in the midportion of the right anterior tibial area for one month. Sympathectomy performed prior to admission had been without benefit. Ether was injected daily for three days; the pain was not lessened and the patient requested discontinuation of the injections because of inebriation which he found to be distressing. It was apparent that nothing could be accomplished by medical treatment and amputation was advised; the patient returned to his home.

**Case 13.**—A man, 38 years of age, was admitted to the hospital because of arteriosclerosis obliterans. Operative procedures prior to admission had consisted in bilateral lumbar sympathectomy, five years previously, and amputation of the left leg, two years previously. For three months he had had an extremely painful ulcer on the right first toe. He had continued to smoke. Ether was injected daily for six consecutive days. Pain was not relieved and the patient refused additional injections. After several weeks of treatment, pain was relieved and the ulcer healed.

**Case 14.**—A man, 58 years of age, was admitted to the hospital because of arteriosclerosis obliterans, diabetes mellitus, and an ischemic ulcer over the left medial malleolus. Ether was injected daily for six days; the patient refused further injections because severe nausea and vomiting followed two injections. Treatment without ether was continued for three additional weeks, at the end of which time the ulcer had healed.

**Case 15.**—A man, 57 years of age, was admitted to the hospital because of arteriosclerosis obliterans. For two months, pain in the right foot had been severe. Treatment with histidine and vitamin C for twenty-one days prior to admission had not caused lessening of the pain. Ether was injected daily for seven days, during which there was gradual lessening of the pain until it was about a half that which had been present on admission. For three days
the patient did not receive ether; seven more daily
injections were then given. During the period of
treatment, the right foot became progressively colder
and an area of gangrene appeared on the right
first toe. Pain recurred; the gangrenous area ex-
tended; there were other signs of extreme ischemia
and amputation of the leg was performed.

Summary of Observations of Cases Reported
in Series D: There was nothing in observation
of any of these cases to indicate that the intra-
venous injection of ether was beneficial. Fail-
ure of relief of pain was striking. There was no
clinical evidence of improvement in arterial
circulation which could be attributed directly
to the intravenous injection of ether. To be
sure, the number of injections was small in
most instances but, in general, the patients did
not desire further injection, a reaction which
leads strong support to our own clinical ob-
servations that the injections were largely or
wholly without value.

Series E. In nine instances, studies of the
temperature of the skin of the digits were made
under basal conditions to determine the effect
of a single injection of ether on blood flow to the
digits. Three of these cases have been previ-
ously recorded as Cases 11, 12, and 14. In 2
of these cases (11 and 12) there was no increase
in the temperature of the skin as a result of the
injection. In Case 12 there was a minor in-
crease in the temperature of the toes during
the injection of ether.

Case 16.—A man, 58 years of age, was admitted
to the hospital because of diabetes mellitus and
arteriosclerosis obliterans with ischemic neuritis
of the right foot of four months' duration. During a
single intravenous injection of ether, under basal
conditions, there was no change in the tempera-
ture of the skin of the markedly ischemic right foot but
the temperature of the skin of the left foot increased
by as much as 4 degrees C. and persisted for an hour
after the infusion was terminated. However, when
the patient was moved into a room the temperature
of which was 32 to 33 C., there was even greater
increase in the temperature of the digits of the left
foot.

Case 17.—A man, 36 years of age, was admitted
to the hospital because of thromboangiitis obliterans.
The left first toe had been persistently red for one
month and there was a small ulcer on its medial
aspect. During the injection of ether the tempera-
ture of the skin of the right toes increased 7 to 8 degrees
C.; the temperature of the skin of the left toes
remained unchanged.

Case 18.—A man, 43 years of age, was admitted
to the hospital because of thromboangiitis obliterans.
Bilateral lumbar sympathectomy had been per-
formed twenty-six years previously. Seventeen
months before admission to the hospital, an ulcer
appeared on the left fourth toe; five months before
admission, an ulcer appeared on the left first toe
after trivial trauma. Prior to admission the patient
had received injections of histidine and vitamin C
two or three times weekly for seven weeks; no
benefit had been apparent. During injection of ether,
under basal conditions, the temperature of the skin
of the left toes increased about 2.5 degrees C.; no
significant change occurred in the temperature of the
skin of the right toes.

Case 19.—A man, 22 years of age, without evi-
dence of impaired arterial circulation, received an
injection of ether under basal conditions. The
temperature of the skin of the toes did not increase
above that of the environment (25.0 to 26.0 C.).

Case 20.—A man, 20 years of age, without evi-
dence of impaired arterial circulation, received an
injection of ether under basal conditions. During
the injection, the temperature of the skin of the
toes decreased steadily to that of the environment
(25.0 to 26.0 C.).

Case 21.—A woman, 20 years of age, whose
peripheral circulation was normal, was given an
injection of ether under basal conditions. There was
a gradual decrease in the temperature of the skin of
the toes.

Summary of Observations of Cases Reported
in Series E: These studies of the effect on the
temperature of the skin of single injections of
ether demonstrate clearly in nine instances
that ether injected intravenously does not im-
prove the peripheral arterial circulation except
in an occasional case. If ether injected in-
travenously were an effective and unquestionable
method of improving the arterial circulation, it
would cause, in each instance, an increase in
the temperature of the skin, inasmuch as im-
provement in the arterial circulation to digits
is invariably associated with an increase in
the temperature of the skin. In the 9 cases
reported in this series, the evidence that ether
injected intravenously caused lessening of the
peripheral arterial circulation was as strong as
the evidence that the procedure caused im-
provement in the peripheral arterial circula-
tion. The conclusion is inescapable: viewed
most optimistically, ether, when injected ac-
cording to the technic previously described, has
little or no value in improving the peripheral
arterial circulation even in subjects whose peripheral arterial circulation is normal and is, therefore, easily increased by such simple measures as a warm environment or the ingestion of alcohol. Indeed, some of the studies are reminiscent of those of the effect of tobacco smoke, which causes impairment of the peripheral arterial circulation.

Conclusions
1. An intravenous injection of 500 mg. of vitamin C followed after an interval by an intramuscular injection of 5 cc. of a 4 per cent aqueous solution of histidine monohydrochloride and a subcutaneous injection of 100 mg. of vitamin C did not cause an increase in digital blood flow as measured by determination of temperature of the skin. Our clinical experience has not confirmed other observations that these agents are useful in the treatment of peripheral ischemia observed in arteriosclerosis obliterans.

2. The intravenous injection of ether had no consistent effect on acral blood flow as measured by the temperature of the skin. In some instances there was evidence of increased blood flow; in other instances there was evidence of a decrease in the acral blood flow. Our clinical experience with the intravenous injection of ether does not indicate that this method is of value in the treatment of ischemia of the extremities in thromboangiitis obliterans and arteriosclerosis obliterans. We were unable to confirm the observations of good results which have been reported previously. Because of unpleasant effects, there was great resistance to repeated injections; some patients refused them. In general, the pain of ischemia was not relieved and there was no improvement in ischemic lesions.

References
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SYDNEY J. WEISMAN and EDGAR V. ALLEN

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