Effects of an Adrenergic Blocking Agent (Dibenzyline) upon Clinical Manifestations of Arterial Insufficiency in the Extremities

By Lothar Wertheimer, M.D., Walter Redisch, M.D., and J. Murray Steele, M.D.

Adrenergic blocking with Dibenzyline measurably enhances the healing of ischemic ulcers. Eleven cases of obliterator arterial disease and two cases of Raynaud's disease were closely observed and are reported in detail. In six of the individuals suffering from obliterator arterial disease, changes in blood flow were documented by plethysmography. Dibenzyline measurably influenced intermittent claudication only after prolonged administration (three to four months) in four out of eight closely observed patients without ulcers. The results of the physiologic tests suggest that during the early phases of adrenergic blocking the increase in blood flow is mostly in the skin, while in the later phases increase in blood flow through the muscle predominates.

In the course of testing the effects upon various vascular beds of certain drugs designed to lower arterial pressure, it has been found by a number of workers that several of these drugs had a tendency to increase the rate of blood flow to the extremities and that some of them did so regularly and markedly. The strong adrenergic blockers, such as the methonium and Dibenamine derivatives, have a marked effect upon peripheral flow.

It seemed, therefore, worthwhile to observe closely a small number of patients suffering from clinical manifestations of arterial insufficiency and to study the behavior of their extremities in response to adrenergic blocking. The drug which we have so far used most extensively in these studies is Dibenzyline. It was chosen in preference to Dibenamine because it can be used orally. Hexamethonium is a strong adrenergic blocker and has a marked effect upon the blood flow to the extremities, but it is also a cholinergic blocker. Its hypotensive action, furthermore, is so great that its use in long-term experiments on normotensive individuals is impractical. Lately study of another Dibenamine derivative which can be used orally (Ilidar) has been undertaken but is not sufficiently far along to deserve reporting. Its action upon extremity flow seems to be similar to that of Dibenzyline. This report is confined to our experiences with Dibenzyline.

Methods and Material

Two gross manifestations of arterial insufficiency, gangrenous ulcer and intermittent claudication, were chosen for observation of their response to prolonged adrenergic blocking. So far studies have been concluded in 28 patients, classified in five groups.

1. Raynaud's disease (two cases): Both patients exhibited ulcerations of many fingers of both hands. Both had been subjected to bilateral sympathectomy with transient improvement which had subsided by the time adrenergic blocking was begun.

2. Thromboangiitis obliterans (two cases): These subjects both were suffering from severe pain and extensive ulceration of the extremities. One had lost both lower extremities, two fingers and three distal phalanges of fingers, and the other had lost one toe and distal phalanges of two toes by the time adrenergic blocking was instituted.

3. Obliterative arteriosclerosis with gangrene (nine cases): All of these patients exhibited gangrenous ulcerations on the lower extremities (toes, heels, lower legs). They manifested all the clinical signs of occlusive peripheral arterial disease. Four of them had lost one lower extremity prior to study.

4. Obliterative arteriosclerosis without gangrene (11 cases): These patients presented the clinical picture of intermittent claudication with or without rest pain. They all exhibited signs of arterial insufficiency such as absence of pulsations, coldness and postural color changes.

5. Ulceration attributed to impairment of venous circulation (four cases): None of these patients ex-
hibited signs of arterial insufficiency. Three of these subjects had leg ulcers attributable to long-standing varicosities, refractory to treatment; one had developed gangrene following trauma complicated by infection and thrombophlebitis.

The patients with Raynaud's disease and those with obliterative arteriosclerosis without gangrene were ambulatory. All of the others were hospital patients confined to bed or wheelchair and had been treated in the usual manner, such as postural adjustment, cleanliness, careful dressing, protection by bandages and cradles, use of antibiotics for secondary infections and drainage of abscesses and removal of dead tissue when necessary. This regime remained unchanged throughout the period included in this report. The smoking habits of the patients with obliterative arteriosclerosis were not changed. In the two patients with Buerger's disease, abstinence from tobacco was ordered. In the first case (JM) little cooperation was obtained. It should be noted, however, that there was no apparent correlation between the patient's smoking and the course of her illness. During several months of the acute suppurative pulmonary complication, she did not smoke at all, but was off Dibenzyline. It was then that she had a severe relapse. The second patient (GMS) had stopped smoking five years before treatment with Dibenzyline was started.

Dibenzyline was given in doses ranging from 20 to 480 mg. per day over periods ranging from three weeks to several months. In roughly half of the cases, Dibenzyline was discontinued one or more times. In about half of these it was replaced by placebos while in the other half no medication was given in the intervals.

The criterion used for the establishment of adrenergic blocking was pupillary response, namely, inability of the pupil to dilate in darkness or with 10 per cent Neo-Synephrine. The dose necessary to produce adequate adrenergic blocking varied widely from individual to individual; some tachyphylaxis seemed to develop in the majority of subjects. The physiologic effects of adrenergic blocking were observed in six subjects by measuring blood flow through the upper extremities plethysmographically and by simultaneously recording surface temperatures in repeated experiments. The reflex responses to warming were also measured. Skin flow and muscle flow were estimated according to a recently published procedure. All experiments were done at 20 C. environmental temperature and 55 per cent humidity.

RESULTS

Group 1. Raynaud's Disease

J. C., a woman 44 years of age, had suffered for 13 years from Raynaud's disease with syncopal attacks, pain and small ulcerations on both upper extremities. Right cervical sympathectomy was performed three and one-half years before the present study began, left cervical sympathectomy two and one-half years before. The effect of sympathectomy started to diminish by spring, 1952. By December 1952, there were ulcerations on most of the fingers. The fingers showed bluish discoloration and sclerodactyia.

J. C. was started on Dibenzyline, 60 mg. a day, in April 1952, with healing of ulcers and remission of pain after four weeks. Subsequently Dibenzyline was discontinued and placebo tablets substituted for six weeks, with recurrence of pain and ulcerations in the third week of placebo administration. Dibenzyline therapy was again started at the same dose and again pain subsided and ulcers healed within three weeks. This cycle has since been repeated once more with the use of placebos in the interval and twice more with no medication in the interval; results were always the same. It was noted, however, that in the last experimental period the ulcers started healing only in the fifth week of medication.

L. R., a man 34 years of age, gave a nine-year history of Raynaud's disease. Right and left cervical sympathectomy performed in 1943 and 1944, respectively, were followed by improvement. By 1948 ulcerations on all 10 fingers had reappeared and were extremely painful. At that time a good response was obtained with Roniacol tartrate, which tapered off after about one year.

L. R. ran a very similar course on the same experimental plan as J. C., starting in September 1952, except that he could not tolerate more than 30 mg. of Dibenzyline a day because of disturbances of his sexual function on higher doses. Nevertheless the ulcers healed after several weeks of therapy only to recur three weeks after discontinuing the drug and to heal again on readministration of Dibenzyline.

Both patients were normotensive and developed mild postural hypotension when on Dibenzyline, with an average drop of 10 to 15 mm. Hg both in systolic and diastolic pressures. Capillary microscopy of the nail bed showed similar findings in both cases: giant loops with short or absent arterial limbs were present, while the transition and venous limbs were enormously enlarged (10 to 20 times the
normal average). There was stasis of blood in about two-thirds of the visualized loops and very slow motion of clumped erythrocytes in the remaining third; the blood column showed deep purplish-blue color.

The following changes were observed to occur regularly in the nail-bed capillaries parallel with gross improvement on Dibenzyline: blood flow became visible in about twice as many loops as before, the column moved much faster and the color was brighter, rather reddish than bluish; arterial limbs of about the same length as the venous limbs became visible on most loops; quantitative measurements of change in diameter of transition and venous limbs were not done but they seemed to become narrower.

Group 2. Thromboangiitis Obliterans

J. M., a woman 50 years of age, gave a history of 23 years' duration, starting with heaviness and pain on walking in both legs, ulcer formation on both feet and amputations of toes. She was a heavy smoker, having started at age 12. In 1934, a diagnosis of Raynaud's disease was made and a Leriche operation was performed on left femoral artery in the same year, and on the right femoral artery in 1936. Rest pain has been present in both legs since 1940. In 1943, when a diagnosis of Buerger's disease was made, she stopped smoking "intermittently." (This situation still prevails.) She was admitted to hospital in July 1952 with tenderness, redness and pitting edema of both feet, impending gangrene of left second toe and an ulcerated amputation site on the left fifth toe. A deep gangrenous ulcer about 2.5 cm. in diameter was present at the base of the right great toe on planter surface and a superficial ulcer on the right heel. Very severe rest pain was present constantly in both lower extremities and somewhat less severe pain in both upper extremities. The patient exhibited all signs of severe arterial insufficiency in both the lower and, to a lesser degree, the upper extremities. The patient had been using codeine and various combinations of analgesics for several years. On admission, heavy sedation was needed. Attempts to substitute placebos for narcotics were unsuccessful. At the time treatment was begun, as much as 350 mg. of Demerol, 100 mg. of codeine, 1.5 Gm. of chloral hydrate and 300 mg. of sodium Amytal in 24 hours was necessary to obtain relief of pain.

The administration of Dibenzyline was begun on Aug. 5, 1952, 60 mg. a day, with rapid increase in dose to 480 mg. a day. By the middle of November 1952, the ulcers had healed on this regimen. At this time the dose was decreased to 360 mg. because of anorexia, dizziness and palpitations. The rest pains, which appeared to be somewhat aggravated during the first six weeks of adrenergic blocking, were markedly diminished by this time and thus permitted the gradual reduction in the amount of narcotic required. At the end of November, the patient developed pneumococcal pneumonia followed by empyema, necessitating surgical drainage. Dibenzyline was discontinued and severe rest pain and ulcerations recurred within a month. A hemorrhagic skin eruption with blebs on both legs led to readministration of Dibenzyline. Starting Jan. 6, 1953, 240 mg. a day were given until discharge on June 4, 1953. By that time all ulcerations had healed, the rest pain had subsided and the use of narcotics had been completely discontinued.

G. M. S., a 47 year old man, gave a history of pain, numbness and coldness of the right, later of the left, foot since 1931 (22 years). Gangrene of the right foot began in 1932. It progressed more rapidly after "sectioning of nerve" in 1933 and necessitated a midthigh amputation of the right leg in 1934. In 1942, injury to the index finger of the left hand, followed by gangrene, necessitated amputation of the finger. Between 1943 and 1946, several amputations of the left lower extremity, the last one being in midthigh, were performed. In 1947, the second and third fingers of the right hand were amputated because of gangrene following injury. He was admitted on Jan. 15, 1953, with gangrene of the right fifth finger and deep gangrenous ulcers on end phalanges of the third and fourth fingers of the left hand. Severe pain and marked inflammatory reaction were present.

Patient was scheduled for amputation when he was started on 60 mg. of Dibenzyline on Feb. 6, 1953. He was treated on the Surgical Service until March, then transferred to the Research Service and treated intensively with 160 mg. of Dibenzyline daily. By June his ulcers were healed. The uppermost tip of the left fifth finger sloughed off, but the finger healed perfectly and appears to be well-supplied with blood. The nail has regrown. His pains started to diminish after about six weeks of adrenergic blocking and have completely subsided.
Group 3. Obliterative Arteriosclerosis with Gangrene

Gangrenous ulcerations which had been under observation for 12 to 80 weeks and which had shown no tendency to heal or had become worse, healed within 4 to 20 weeks after administration of Dibenzyline had been started.

In five of the nine cases reported, the drug was discontinued immediately after healing had taken place. The recurrences were again treated successfully. The daily dose was 60 to 200 mg. (table 1).

<table>
<thead>
<tr>
<th>Name</th>
<th>Age</th>
<th>Sex</th>
<th>Description of Lesions</th>
<th>Duration of Lesions before Adrenergic Blocking</th>
<th>Daily Dose of Dibenzyline</th>
<th>Result</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>G. G.</td>
<td>70</td>
<td>f</td>
<td>Deep round half-dollar size gangrenous ulcer on lateral border of left foot. Severe inflammation</td>
<td>16-20 wks.</td>
<td>100 mg.</td>
<td>Healing within 10 wks.</td>
<td>Pain completely subsided after about 2 wks. of adrenergic blocking</td>
</tr>
<tr>
<td>S. K.</td>
<td>60</td>
<td>m</td>
<td>Gangrene of left heel with deep ulceration extending down to tendon, 2 X 3½ cm. Severe inflammation</td>
<td>About 30 wks.</td>
<td>60 mg.</td>
<td>Healing within 8 wks.</td>
<td>Recurrence of ulceration after discontinuation of treatment. Renewed healing after resumption of therapy</td>
</tr>
<tr>
<td>J. K.</td>
<td>68</td>
<td>m</td>
<td>Gangrene with 1 X 1 cm. ulcer; hyperkeratotic crust; right external malleolus</td>
<td>50-60 wks.</td>
<td>80-180 mg.</td>
<td>Healing within 12-20 wks.</td>
<td>Severe pain subsided only after 4 mos. Seven months later pain but not ulceration recurred and medication was resumed with success</td>
</tr>
<tr>
<td>M. B.</td>
<td>62</td>
<td>m</td>
<td>2 gangrenous ulcers 10 X 5 cm. and 6 X 5 cm. longitudinally on outer aspect of right calf. Extremely severe inflammation</td>
<td>12 wks.</td>
<td>60 mg.</td>
<td>Healing within 4-5 wks.</td>
<td>Treatment discontinued twice (once replaced by placebo) with recurrence within 2 wks. and renewed healing several weeks after reinstition of therapy</td>
</tr>
<tr>
<td>A. M.</td>
<td>62</td>
<td>m</td>
<td>2 gangrenous ulcers 3 X 4 cm. each, one on each heel, extending down to muscle. Gangrene of distal phalanx left 4th toe. Severe inflammation</td>
<td>70-80 wks.</td>
<td>200 mg.</td>
<td>Healing within 16-20 wks.</td>
<td>Severe pain completely subsided after about 3 wks. of adrenergic blocking</td>
</tr>
<tr>
<td>W. C.</td>
<td>66</td>
<td>m</td>
<td>Circular dry gangrene 2½ cm. diameter. Surrounding inflammation</td>
<td>8 wks.</td>
<td>60 mg.</td>
<td>Healing within 6-8 wks.</td>
<td>Ulcer recurred 3 wks. after drug was stopped. On resumption of therapy ulcer healed in 4 wks. Patient is diabetic</td>
</tr>
<tr>
<td>I. G.</td>
<td>63</td>
<td>m</td>
<td>Gangrene of 2nd and 3rd right toes extending to a semi-circular area at the plantar aspect, 6 cm. in diameter with inflammation</td>
<td>20 wks.</td>
<td>60-100 mg.</td>
<td>Arrest of gangrene with mummification within 7 wks.</td>
<td>Treatment was discontinued; gangrene extended; pain and inflammation recurred. Treatment resumed with improvement. Patient is a diabetic</td>
</tr>
<tr>
<td>M. O'B.</td>
<td>63</td>
<td>m</td>
<td>Large gangrenous ulcers, of middle and terminal phalanges of 2nd and 3rd right toe and end phalanx of right big toe, with inflammation and blistering</td>
<td>15 wks.</td>
<td>60-120 mg.</td>
<td>Healing complete within 8 wks.</td>
<td>Case still under observation. Ulcer has remained healed 6 mos. Patient is diabetic</td>
</tr>
<tr>
<td>J. J.</td>
<td>60</td>
<td>f</td>
<td>Deep gangrenous ulcer half-dollar size, plantar surface of left foot</td>
<td>16-20 wks.</td>
<td>120 mg.</td>
<td>Healing within 10 wks.</td>
<td>Case still under observation. Ulcer has remained healed for 7 mos.</td>
</tr>
</tbody>
</table>
**Group 4. Obliterative Arteriosclerosis without Gangrene**

Objective measurements for potential improvement were employed in eight patients. Since the exercise involved in repeated measurements of claudication time has, in itself, been reported to cause improvement, three additional cases were evaluated subjectively only.

Four patients showed unequivocal objective improvement after 12 weeks or more of treatment with Dibenzyline in doses ranging from 60 to 180 mg. per day. Their ability to walk improved from one-half to two blocks initially to 5 to 10 blocks. Average claudication time measured on the stationary bicycle rose from 50 to 100 seconds initially to 200 to 400 seconds. Subjective improvement was noted in the three patients to whom Dibenzyline was given but who were not subjected to the regular series of objective tests. The remaining four failed to give clear objective evidence of improvement even after treatment for three months or more. Likewise these subjects evidenced little or no subjective improvement.

**Group 5. Ulceration Attributed to Impairment of Venous Circulation**

This group turned out to represent a sort of control group for the previous groups in whom the arterial blood supply was obviously impaired. There was no real improvement in any of the three cases with ulcers which were thought to be due to impaired venous return on prolonged administration of Dibenzyline in doses from 120 to 360 mg. per day. This observation is of some interest in view of the fact that these ulcers seemed much more superficial than many of the ulcers in the previous groups. In the fourth case (gangrene, following trauma), no benefit was derived from adrenergic blocking continued for four and one-half weeks with the daily administration of 120 mg. of Dibenzyline. It was consequently necessary to amputate the extremity.

**Physiologic Documentation**

It will be noted (table 2) that after four weeks of adrenergic blocking the average skin temperature of toes had risen significantly, but returned to almost the basic values after three to five months of continued adrenergic blocking; blood flow through the skin showed a similar pattern of response (table 2). In contrast, blood flow through the muscle showed no significant change after four weeks (except for a slightly decreased reflex response to warming), while there was a measurable increase in muscle flow after three to five months.

**DISCUSSION**

Haimovici was the first to report the clinical use of Dibenzyline in peripheral vascular disease. He noted that during administration of the drug to two cases of Raynaud’s disease the

**Table 2.—Effects of Adrenergic Blocking with Dibenzyline on Blood Flow to Skin and Muscle**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Skin Temp. of Toes (°C)</th>
<th>Max. Reflex Response of Skin Temp. to Warming (°C)</th>
<th>Rate of Blood Flow through Skin (ml./100 ml. tissue min.)</th>
<th>Max. Reflex Response of Blood Flow through Skin to Warming (ml./100 ml. tissue min.)</th>
<th>Rate of Blood Flow through Muscle (ml./100 ml. tissue min.)</th>
<th>Max. Reflex Response of Blood Flow through Muscle to Warming (ml./100 ml. tissue min.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base line</td>
<td>22.0 (19.5-23.5)</td>
<td>26.5 (22.5-28.5)</td>
<td>1.6 (0.5-2.9)</td>
<td>15.1 (10.8-24.8)</td>
<td>1.3 (0.4-2.1)</td>
<td>7.9 (6.2-10.4)</td>
</tr>
<tr>
<td>After 4 weeks of adrenergic blocking</td>
<td>26.5 (24.0-33.5)</td>
<td>30.5 (28.5-35.0)</td>
<td>2.8 (0.5-4.1)</td>
<td>18.6 (15.6-22.2)</td>
<td>1.0 (0.4-1.4)</td>
<td>4.4 (2.0-7.4)</td>
</tr>
<tr>
<td>After 12-20 weeks of adrenergic blocking</td>
<td>22.5 (20.0-25.5)</td>
<td>25.5 (23.0-32.5)</td>
<td>1.8 (0.6-2.0)</td>
<td>14.4 (12.0-15.8)</td>
<td>2.6 (1.6-2.9)</td>
<td>8.0 (4.8-12.5)</td>
</tr>
</tbody>
</table>
Wertheimer, Redisch, and Steele

The typical response to cold could no longer be elicited. Moser and co-workers\textsuperscript{11} reported favorable results with Dibenzyline, hexamethonium and Priscoline in vasospastic conditions (causalgia, Raynaud’s syndrome); they also treated 10 cases of “traumatic or postoperative arterial insufficiency,” 10 cases of thromboangiitis obliterans and eight cases of arteriosclerosis obliterans, with less favorable results. No details are given, and there is no mention of trophic disturbances, ulcer formation or other forms of local tissue necrosis.

The clinical observations presented here have been taken by us to constitute solid evidence that the drug Dibenzyline favorably influenced the healing of ulcerations due to obliterative arterial disease. Physiologic evidence of increased blood flow during the period of administration of the drug was obtained in a small number of these subjects. It seems justified from these observations to conclude that the continuous afflux of adrenergic impulses to the collateral circulation in limbs with grossly impaired primary circulation plays a large role in preventing the healing of ischemic ulcers. Continued blocking of adrenergic impulses to the blood vessels promotes the healing of the ulcers to a degree which has not been observed following sympathectomy or ganglionic blocking. The doses necessary for the prompt healing of small ulcers in the two cases of Raynaud’s disease were conspicuously smaller than the amounts which had to be used in cases of obliterative arterial disease.

The effect of adrenergic blocking with Dibenzyline upon intermittent claudication is much less impressive than that upon the healing of ulcers, at least within the first four or six weeks of therapy, probably because within the first few weeks the effect of the drug upon blood flow to the skin is marked, while muscle flow is not influenced (table 2). After 12 to 20 weeks, there is also a definite increase in blood flow through the muscular tissues. Circulation to the skin is primarily affected; only on prolonged administration for many weeks or months is an effect upon circulation through the deeper tissues noted. These findings would seem to indicate that Dibenzyline therapy for this type of case should be maintained for at least 12 weeks. Earlier discontinuance of the drug precludes a clear estimation of its efficacy.

Of considerable interest is the observation that ulcers which were not due to impairment of arterial supply did not respond to adrenergic blocking (three cases thought due to impairment of venous return and one of gangrene following trauma). The lack of improvement in this group strengthens the conclusion that it is the improvement in arterial blood supply as a result of adrenergic blocking and not some other unknown factor which affects the healing of ischemic ulcers.

The observations on the nail-bed capillaries of the two cases of Raynaud’s disease are of some interest: the type of capillary loops seen here has been described as a characteristic finding in Raynaud’s disease by some workers\textsuperscript{12, 13} and in generalized scleroderma by Mueller and co-workers.\textsuperscript{14} Acrosclerosis is a quite constant feature in late severe cases of Raynaud’s disease\textsuperscript{15, 16} and the cases of scleroderma in whom this type of capillary loop was described in the literature gave an early history of “Raynaud’s attacks” and later developed trophic disturbances and small ulcers. The changes in the skin capillaries seem quite impressive but their significance remains obscure.

The unwanted side effects of Dibenzyline have been discussed elsewhere. In this study, the following side effects were of major concern: tachycardia, the occasional occurrence of auricular fibrillation, and, in two patients, the development of prolonged dizziness and confusion, alleviated by discontinuation of the drug. These symptoms are sufficiently severe to proscribe treatment in about 1 in 15 individuals. Postural hypotension, headaches, urinary retention, disturbances in ejaculation and gastrointestinal irritation have occurred occasionally, but were never serious enough to exclude a patient from treatment. Disease of the respiratory tract has been pointed out as a contraindication to the use of adrenergic blocking agents; one patient was eliminated from this
study because two attempts at adrenergic blocking were followed by severe asthmatic attacks.

Summary
1. Twenty-four cases with severe impairment of arterial blood flow to the extremities were studied for their response to adrenergic blocking with Dibenzyline.
2. The healing of ischemic ulcerations in two cases of Raynaud's disease, two cases of obliterator thromboangiitis and nine cases of obliterator arteriosclerosis was markedly enhanced; in two cases with gangrene of the toes, necrobiosis was arrested and the gangrene kept dry and mummified.
3. In contrast, ulcerations due to venous stasis and traumatic gangrene in the absence of obvious arterial insufficiency were not influenced in the four cases studied.
4. Objective improvement of intermittent claudication was demonstrated in four out of eight cases of obliterator arteriosclerosis without ulcerations. Subjective improvement was noted in three additional cases. It is stressed that improvement occurred only upon prolonged administration of Dibenzyline. These results appeared to be correlated with physiologic findings that increased blood flow through muscle appeared only after 12 or more weeks of medication.
5. The clinical effects of adrenergic blocking are accompanied by increased blood flow to the extremities as demonstrated by plethysmography and measurement of surface temperatures.

Sumario Español
1. Veinte y cuatro casos con severo deterioro de circulación arterial a las extremidades fueron estudiados de acuerdo a su respuesta a bloqueo adrenérgico con "Dibenzyline."
2. La cicatrización de ulceraciones isquémicas en dos casos de la enfermedad de Raynaud’s, dos casos de tromboangiitis obliteratora y nueve casos de arterioesclerosis obliteratora fue marcadamente aligerada; en dos casos con gangrena de los dedos del pie, la necrobiosis fue arrestada, la gangrena se mantuvo seca y momificó.
3. En contraste, ulceraciones debidas a estasis venoso y gangrena traumática en ausencia de insuficiencia arterial obvia no fueron influenciadas en cuatro casos.
4. Mejoría objetiva de claudicación intermitente fue demostrada en cuatro de ocho casos de arterioesclerosis obliteratora sin ulceraciones. Mejoría subjetiva se notó en tres casos adicionales. Se enfatiza que la mejoría ocurrió solamente después de la prolongada administración de el "Dibenzyline". Estos resultados parecen estar correlacionados con los hallazgos fisiológicos de que el aumento en circulación a través del músculo apareció solamente después de 12 o más semanas de medicamento.
5. Los efectos clínicos de bloqueo adrenérgico son acompañados por un aumento en circulación a las extremidades como se ha demostrado por medio de plethysmografía y determinación de temperaturas de superficie.

References
3. Moore, P. E., Richardson, A. W., and Green, H. D.: Effects of a new dibenazepine derivative, RO 2-3248, 6-allyl-6,7-dihydro-5H-dibenzo (c,e)azepine phosphate upon the blood flow, the peripheral resistance and the response to injections of epinephrine of the innervated hind limb of the dog. J. Pharmacol. and Exper. Therap. 106: 14, 1952.
7. Redisch, W., Texter, C. T., Jr., Howard, R. M., Stillman, P. H., and Steele, J. M.: The action of SKF 688A (phenoxethyl derivative of dibenamine) upon certain functions of


16 —, and Pickering, G. W.: Observations upon maladies in which the blood supply to digits ceases intermittently or permanently and upon bilateral gangrene of digits; observations relevant to so-called “Raynaud’s disease.” Clin. Sc. 1: 327, 1934.
Effects of an Adrenergic Blocking Agent (Dibenzyline) upon Clinical Manifestations of Arterial Insufficiency in the Extremities

LOTHAR WERTHEIMER, WALTER REDISCH and J. MURRAY STEELE

Circulation. 1954;10:366-373
doi: 10.1161/01.CIR.10.3.366

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1954 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/10/3/366