Inositol and Mannitol Hexanitrites in Hypertension Management

By Lionel M. Bernstein, M.D., Ph.D. and A. C. Ivy, M.D., Ph.D.

This clinical study was undertaken because the clinical literature dealing with the use of mannitol and inositol hexanitrate and to a large extent other nitrates and nitrates which have been used in the management of hypertension fails to consider the development of tolerance. It was found that tolerance to the vasodilator action of mannitol and inositol nitrate develops in from 8 to 14 days and is lost completely within 10 days after withdrawal of the drug. The use of these nitrates should be carefully individualized by determining the optimal dose and the period required for the development and loss of tolerance.

Quickly acting nitrates and nitrates have been used for decades for the relief of angina pectoris. By physiological methods it can be demonstrated that these drugs increase coronary blood flow provided the blood pressure is not reduced too much by a too large dose of the drug and the coronary vessels have not lost their capacity to dilate.

The more slowly acting nitrates and nitrates, especially the organic nitrates, have been and still are used extensively in the management of hypertension. They have been and are used more or less continuously to reduce the blood pressure on the assumption (A) that the hypertension is due to excessive peripheral vasoconstriction, some of which at least may be counteracted by the vasodilator effect of these compounds, and (B) that they are symptomatically beneficial.

This study was undertaken primarily (1) to determine the blood-pressure reducing effectiveness of a new compound, inositol hexanitrate and (2) of an old compound, mannitol hexanitrate, and (3) to ascertain if tolerance develops to the blood-pressure reducing effects of these two compounds. Because tolerance might develop, the study was not designed to examine critically the clinical effectiveness of the drugs or the best way to administer the drugs so as to avoid the development of tolerance, and in that way really test the value of these long-acting nitrates in the management of the hypertensive patient on the basis of the assumption that a reduction of blood pressure is symptomatically and prophylactically valuable. The clinician (L. B.) giving the medication, including a placebo, and supervising the patients did not know the entire purpose of the study and did not know the identity of the tablets.

Literature

We have been unable to find in the literature a carefully designed study to test the assumption that a reduction of blood pressure in the hypertensive patient by the use of nitrates or nitrates is symptomatically and prophylactically valuable. This is primarily because no clinical investigator has considered adequately the development of tolerance to the blood-pressure reducing effects of the compound they used. This has occurred, even though some textbooks of pharmacology, have since 1917, pointed out that tolerance to the blood-pressure reducing effects of nitrates and nitrates appears in a few days, is well-established in two to three weeks and that cessation for several days invariably re-establishes the original extent of susceptibility.

Tolerance to nitroglycerine was apparently first observed in 1888. As early as 1898, Laws described the development of tolerance among the employees of the manufacturers of nitroglycerine. It was referred to again in the American literature in 1905.

In 1909, Mathew published a well conceived study of the blood-pressure reducing effects of several nitrates and nitrates in patients with hypertension. He found that once repeated use tolerance to nitroglycerine develops in 24 hours, to sodium nitrite (0.12 to 0.2 Gm., three times a day) partially in two weeks. He failed to observe tolerance to erythrol nitrate (0.06 Gm., three times a day) and to mannitol hexanitrate (0.06 Gm., three times a day) when prescribed for long periods. Wallace and Ringer, who carefully

From the Department of Clinical Science, University of Illinois College of Medicine, Chicago, Ill.

Circulation, Volume XII, September, 1955
studied the blood-pressure reducing effects of several nitrates and nitrites, as regards latent period of action, extent and duration of the decrease in blood pressure, did not study tolerance (for a table giving such data see references 1 and 9). A number of clinicians prior to 1915 reported on the use of nitrates in the management of hypertension without mentioning the subject of tolerance.10, 11

During World War I, attention was again directed to the tolerance developed by persons making nitroglycerin,15, 11 (Some munition workers develop a tolerance readily and others do not; the latter usually discontinue such work.) But, prior to 1929 a carefully controlled study of the tolerance and cross tolerance to nitrates and nitrites had not been conducted. Then, Meyers and Austin24 found that rabbits developed within several days a definite tolerance to the blood-pressure reducing effects of sodium nitrite with a cross-tolerance to nitroglycerin. Crandall16 found that dogs made tolerant to amyl nitrite are tolerant to the vascular effects of sodium nitrite. Crandall, Leake, Loevenhart, and Muehlberger57a using normal human subjects found that a tolerance to the headache-producing effect of the nitrates and nitrites developed faster than to the blood-pressure reducing effect. The ease of developing some tolerance to one headache dose ranked in order as follows: amyl nitrite (2 to 3 hours), methyl nitrate (24 hours), ethylene glycol dinitrate (32 hours), glycerol trinitrate (38 hours), and erythrol tetranitrate (60 hours). Cross tolerance was demonstrated. They failed to observe the development of tolerance to the vascular effects of sodium nitrite (0.22 Gm. two times a day) in four days in man and in six days in a dog (0.3 Gm., two or three times per day). In two subjects, however, tolerance to the vascular effects of sodium nitrite were abolished by rendering them tolerant to ethylene glycol dinitrate.

Since 1924, 119, 1626 monographs or textbooks, and ten27-16 articles dealing with the treatment of hypertension reviewed by us do not mention the possibility of tolerance developing, and in that way annulling the potential benefit of the prolonged use of nitrates and nitrites. One author27 of a pedagogical article mentions the possibility of tolerance developing to all nitrates and nitrites as the subject is presented in textbooks of pharmacology.1-2

The literature clearly establishes that adequate doses of the nitrates or nitrites usually employed therapeutically reduce blood pressure of normal subjects, the extent depending on the dose and the susceptibility of the subject.1, 2, 7, 8, 14, 15 The susceptibility of patients with hypertension varies widely.7, 8, 11, 29, 30, 34, 36, 38 Some patients are very sensitive, and collapse or a postural hypotension may occur.39 In such patients the action of the drug is primarily on the venous side causing a pooling of the blood in the veins, a decreased cardiac output, and an increase in central vasoconstrictor tone.39 In some patients there is no change or there may even be a rise in blood pressure41 with ordinary doses. The effect on urinary output also varies widely in different patients.11, 27, 34, 39

Therapeutically there is no evidence indicating that the daily use of the nitrates or nitrites modifies the course of hypertensive disease. Except for the benefit derived from the cautious use of the quickly and short-acting nitrates and nitrites for the relief of angina pectoris, most authors today either are skeptical regarding, or deny, their value in the management of the symptoms of hypertension. This is the view which would logically develop in the case that tolerance developed within a week or two after starting a slow acting drug. A drug such as bismuth subnitrate could at first give some symptomatic relief due to a small blood pressure decreasing effect which could then be continued as a psychotherapeutic effect after the development of tolerance. Thus, one observer could report an improvement42 and other observers could report that the compound had no more effect than a placebo or frequent office calls.25, 33, 34

Regarding mannitol hexanitrate, Mathew7 wrote: "With it I have not observed the same individual susceptibility or any tendency to unpleasant effects, probably owing to the fact that it produces its maximum effect much more slowly than erythrol." He advised that the dose should be individualized by determining the dose which lowers blood pressure without causing undesirable symptoms. He observed no evidence of tolerance, though one cannot be certain from his article how carefully he checked to ascertain how regularly his patients took the drug. Evans and Loughman34 reported that the use of mannitol hexanitrate had no greater beneficial effect than a placebo. However, their patients reported to them only every two weeks, and hence the development of a tolerance may have been overlooked. Weaver, Wills, and Hodge25 studied 19 hypertensive patients, eight of whom received mannitol hexanitrate (30 mg., three times per day) and 11 a control placebo. Side effects were not seen in 28 patients receiving the 30-mg. dose for varying periods of time. The placebo therapy did not produce symptomatic relief similar to that obtained with the drug. These observers, however, reported that the symptomatic relief occurred without a fall in blood pressure. (A) Does this mean that relief was obtained for a few days due to the vascular effect of the drug and that, then, a tolerance developed and a psychotherapeutic effect appeared? (B) Or, does it mean that relief may actually be obtained without a lowering of blood pressure as occurs sometimes in angina pectoris after taking nitroglycerin or amyl nitrite?27

A 30 to 60-mg. dose of mannitol hexanitrate orally starts to lower blood pressure after a latent period of 15 to 30 minutes; produces a fall in systolic pressure of from 10 to 50 mm. Hg, which becomes maximum in from 60 to 120 minutes; and
disappears in from four to six hours. It increases coronary flow in the perfused rabbit’s heart. There are no reports published to our knowledge on the effect of inositol hexanitrate on blood pressure.

This review indicates that further evidence on the development of tolerance to the slow-acting nitrates and nitrites is needed, and that a study of their symptomatic effectiveness in which the factor of tolerance, as well as psychotherapeutic effects, is considered has not been performed.

**Experimental Design**

All the 32 hypertensive patients were ambulatory and for the most part asymptomatic. Such patients were selected because the objectives of the investigation were to test the hypotensive action of a new organic nitrate and to ascertain whether tolerance developed to mannitol hexanitrate and the new nitrate, inositol hexanitrate.

To exclude patients with other diseases, a complete history and physical examination as well as the following laboratory tests were performed: a complete blood cell and hemoglobin study; serology; urinalysis; blood plasma nonprotein nitrogen; renal urea clearance and/or concentration-dilution test; electrocardiogram, 12 leads; and chest x-ray films.

All subjects had urea clearances greater than 55 per cent of normal, or had urine concentrations greater than 1:022. Cardiac enlargement was present in 16 patients; dilation and tortuosity of the aorta in five; and cardiac enlargement and aortic dilatation in four. Seven patients had normal sized hearts; 12 had normal electrocardiograms. Of the 20 patients with abnormal electrocardiograms, 10 showed left ventricular hypertrophy and/or strain patterns; eight showed nonspecific abnormal patterns; and two right bundle branch block patterns. Additional laboratory tests were performed on individual patients when indicated to investigate complaints not related to hypertension.

In order to avoid completely all prejudice, a “blind-placebo plan” of study was undertaken. At no time in the study did the clinical investigator know the identity of the three tablets used. He was instructed to give the three tablets to alternate patients as they became a member of the study group and to make certain observations with the objective that after several months the observations would show a difference or similarity in the action of the three tablets.

At each visit, the patient sat in a waiting room for approximately 30 minutes before entering the consultation room. The subjective complaints were discussed and recorded. The blood pressure was then determined to the nearest 5 mm. Hg mark in sitting, supine, and standing positions in the left arm and then on the right arm. In this report the pressure taken in the right arm in sitting position was arbitrarily chosen for comparisons. Thus, the value used was one which in all subjects followed sitting in the waiting room and the same changes of position during three blood pressure determinations.

The tablets were labeled X, Y, and Z. They contained respectively 30 mg. mannitol hexanitrate, placebo, and 10 mg. inositol hexanitrate. The dose was increased by changing the number of tablets taken.

Analyses of the data were performed by the analysis of variance technique.

Other details of the procedure will be given under the results.

**Observations**

**Part I. On the basis of blood pressure and clinical response can one in a “blind” or “unknown” test differentiate between the results with a placebo tablet and tablets containing a slow acting nitrate?**

**Procedure:** After two control visits and blood pressure determinations, the patients alternately were first placed on tablet X, or Y, or Z, and were instructed to take two tablets four times daily or every four hours while awake. On the next visit, two weeks later, the patient returned the unused portion of his initial medication to make certain that the directions had been followed, and a supply of a second medication was given. These medications were given in random sequence to each patient, allowing each patient to serve as his own control. Thus, the patient was rotated from tablet X to Y, to Z, etc. In this way, the results on those patients who left the study group after a few months were still of value, since observations on the effect of each medication on them had been made. Those patients who continued in the group had several observations on each medication. In general, after two weeks on each of the three tablets, the patients were rotated on each medication for four weeks, then rotated on each at higher doses. This procedure excluded variations in blood pressure and symptoms due to changes of season. The general effects of temperature, barometric pressure, humidity, snow, rain, and any number of subtle and unknown factors on blood pressure were nullified by the fact that on any given clinic day different patients were given different medications; that is, during any single period some patients were taking tablet X, others tablet Y, and still others tablet Z.

**Results:** In our tables and statistical analyses the number of blood pressure determinations was the same for each medication. Since the initial dosage level was two tablets, and then the number of tablets was increased in order to attempt to obtain a greater effect on the patient’s blood pressure level, several dosage levels were used. To simplify the presentation
and analysis of the data, the doses on all the patients were arbitrarily divided into two
groups, namely, a “low dosage group” (two
to six tablets four times daily) and a “high
dosage group” (9 to 12 tablets four times daily).

In the “low dosage group”, there were 130
complete series of determinations on each of
the three tablets on 32 patients. The mean
systolic pressures in mm. Hg for the three tab-
lets were: X = 198.3; Y = 197.3; and Z = 198.4;
the respective mean diastolic pressures being
111.1, 110.7, and 111.2. There obviously
is no statistically significant difference in these
pressures (tables 1 and 2). Since we know (vide
infra) that the two nitrates on a single administra-
tion in the range used causes a fall in blood
pressure, the failure to find a fall can only be
due to the development of tolerance.

In the “high dosage group” there were 59
complete series of determinations on 16 pa-
tients. The mean systolic pressures in mm.
Hg for the three tablets were: X = 198.5;
Y = 206.6; and Z = 202.3; the respective
mean diastolic pressures were 111.3, 115.2,
and 113.8. The differences between the systolic
and diastolic pressures in the determinations
made while on the nitrates were significantly
lower (tables 3 and 4). Though the differences
are statistically significant, they would not
appear to be clinically significant because they
are relatively so small. Again the existence of
tolerance is evident, in view of the huge doses
administered.

**Table 3.—The Relationship of Systolic Pressure to
“High” Doses of Tablets X (Mannitol Hexanitrate),
Y (Placebo), and Z (Inositol Hexanitrate)**

<table>
<thead>
<tr>
<th>Variance source</th>
<th>Degrees of freedom</th>
<th>Sums of squares</th>
<th>Mean square</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Between patients</td>
<td>15</td>
<td>106,574</td>
<td>7,105</td>
<td>29.9</td>
</tr>
<tr>
<td>Between Y and</td>
<td>1</td>
<td>1,526</td>
<td>1,526</td>
<td>6.4</td>
</tr>
<tr>
<td>(X + Z).....</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Between X and Z.</td>
<td>1</td>
<td>429</td>
<td>429</td>
<td>1.8</td>
</tr>
<tr>
<td>Residual error..</td>
<td>150</td>
<td>37,802</td>
<td>238</td>
<td></td>
</tr>
<tr>
<td>Total..........</td>
<td>176</td>
<td>146,331</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The systolic pressure was significantly lower on
(mannitol plus inositol hexanitrate) treatments than
on placebo treatment (p < .01). There was no signific-
ificant difference between the systolic pressures on the
mannitol and inositol hexanitrates.

**Table 4.—The Relationship of Diastolic Pressure
to “High” Doses of Tablets X (Mannitol Hexanitrate),
Y (Placebo), and Z (Inositol Hexanitrate)**

<table>
<thead>
<tr>
<th>Variance source</th>
<th>Degrees of freedom</th>
<th>Sums of squares</th>
<th>Mean square</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Between patients</td>
<td>15</td>
<td>30,873</td>
<td>2,058</td>
<td>36.1</td>
</tr>
<tr>
<td>Between Y and</td>
<td>1</td>
<td>1,397</td>
<td>1,397</td>
<td>24.5</td>
</tr>
<tr>
<td>(X + Z).....</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Between X and Z.</td>
<td>1</td>
<td>204</td>
<td>204</td>
<td>3.58</td>
</tr>
<tr>
<td>Residual error..</td>
<td>150</td>
<td>9,033</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>Total..........</td>
<td>176</td>
<td>41,507</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The diastolic pressure was significantly lower on
(mannitol plus inositol hexanitrate) treatments than
on placebo treatment (p < .001). There was no signific-
ificant difference between the diastolic pressures on the
mannitol and inositol hexanitrate treatments.
effects on the blood pressure of hypertensive patients on repeated daily use of the nitrates or nitrates as those obtained with a placebo. Apparently those who have failed to observe tolerance develop when these organic nitrates were used did not control their patients adequately so that the medication was taken sufficiently regularly to cause the development of tolerance.

In order to test this interpretation of the foregoing observations two other series of experiments were performed.

**Part II. What is the effect on blood pressure of mannitol and inositol hexanitrate when given in a single dose?**

**Procedure:** Six of our hypertensive patients whose blood pressure had been found repeatedly not to be lowered by relatively huge doses of mannitol and inositol hexanitrate were used in this experiment. Before using them all nitrate medication was discontinued for four weeks. Then, rotating at two week intervals a single dose of 12 tablets of mannitol (0.36 Gm.) and inositol (0.12 Gm.) hexanitrate and placebo were administered to each subject. The blood pressure was then determined at intervals up to four and one-half hours.

**Results:** The results, as averages, are graphed in figure 1. It will be noted that the placebo had no effect over a period of four and one half hours. The mannitol (0.36 Gm.) produced a marked fall in systolic (64 mm. Hg) and diastolic (32 mm. Hg) pressure which had not returned to the control pressure after four and one half hours. The inositol (0.12 Gm.) produced a decided fall in systolic (44 mm. Hg) and diastolic (20 mm. Hg) pressure which had not returned to the control pressure after four and one half hours.

**Fig. 1.** Showing the response of the systolic and diastolic blood pressure of hypertensive patients to a placebo and to mannitol and inositol hexanitrate.

**Part III. What period of time is required to produce tolerance to mannitol and inositol hexanitrate?**

**Procedure:** Fifteen hypertensive patients served as subjects. They were divided into two groups. One group consisted of eight patients whose systolic and diastolic blood pressures were greater than 150 and 100 mm. Hg, respectively. The second group consisted of seven patients whose systolic and diastolic pressures were under 150 and 100 mm. Hg, respectively.

Each patient was given a single dose of 12 tablets of each medication and the blood pressure was determined for a period of four hours. Twelve tablets four times per day were then administered, five of the 15 patients receiving tablet X, five tablet Y, and five tablet Z. The blood pressure of each of the 15 patients was taken on the second, third, fourth, sixth, and eighth days. The medication was then stopped for two weeks. Then the patients were given a new tablet. This was repeated until each of the 15 patients had received each tablet for a period of eight days, each period being broken by a two-week period of no medication.

**Results:** Reference to figure 2 shows the averaged results on the first group of 8 patients. Figure 3 shows the results on the second group of seven patients.

In the first group (fig. 3), it will be noted the tolerance to mannitol and inositol developed in eight days. In the second group, the results with inositol were variable, but tolerance to the mannitol was present but not complete at eight days.

The tolerance is apparently completely absent after discontinuing the drugs for 14 days. In a few patients who had neglected, we found, to take their medication for 10 days, tolerance had been completely lost.

**Side Reactions:** Side reactions, such as headaches, dizziness and palpitation, occurred when the dosage level was suddenly increased above the level of the tolerance which had been developed. In those cases where a small dose such as 60 mg. four times daily, was given and slowly increased to 0.4 Gm. of mannitol four times daily, there were no symptoms or the symptoms were minimal. A few patients were apparently unable in a period of one month to develop a complete tolerance to 0.4 Gm. of mannitol four times per day. Some patients who had not developed a tolerance to the
Fig. 2. Showing the development of tolerance to mannitol and inositol hexanitrate in eight patients whose systolic and diastolic blood pressures were greater than 150 and 100 mm. Hg, respectively.

Fig. 3. Showing the development of tolerance to mannitol and inositol hexanitrate in seven patients whose systolic and diastolic pressures were under 150 and 100 mm. Hg, respectively.

larger doses, developed mild anorexia; one such patients developed “bloating”. One patient regularly, and two other patients occasionally, developed ventricular ectopic beats when taking 0.4 Gm. of mannitol hexanitrate. One patient developed an erythematous, papular, pruritic skin eruption involving the arms and hands while taking 0.28 Gm. of mannitol hexanitrate four times per day. The eruption subsided completely within one week after termination of the medication. Another patient complained of a transient pruritus of the arms while taking 60 mg. of inositol hexanitrate.

Angina: In three patients who had frequent attacks of angina the frequency of the attacks was not affected, as might be anticipated in view of the development of tolerance. In these patients a cross-tolerance to nitroglycerin was observed in that the usual tablet of nitroglycerin sublingually was less effective in abolishing the angina.

No methemoglobinemia was detected spectroscopically while giving the nitrates at any dosage level.

Since most of the patients taking part in this study were asymptomatic, more subjective complaints were recorded when they received the nitrates than the placebo. It should be emphasized, however, that this investigation was not designed for such a purpose. If it had been patients with symptoms would have been selected and the drugs administered so as to have avoided the development of complete or almost complete tolerance.

DISCUSSION

Since tolerance to mannitol and inositol hexanitrate develop and since they decrease systolic and diastolic blood pressure in adequate doses, no clinical investigation that we have been able to find has used them properly in hypertensive patients to test the assumption that the reduction in such patients is symptomatically, if not prophylactically beneficial.

Our results show, we believe, that these organic nitrates when used should be used as is indicated in current textbooks of pharmacology\(^1\). Furthermore, our results show that unless the dose is individualized, as first suggested by Mathew,\(^2\) these drugs are not being properly used. This applies both to the determination of the size and frequency of the initial dose which will lower blood pressure without producing undesirable side reactions and to the determination in each patient of the time required to develop tolerance to that dose and to lose the tolerance.

It would be important both from a clinical and pharmacological point of view to determine in each of a group of patients whether any symptomatic relief obtained during the period of the development of tolerance on the drug would carry over during a four- to five-day period while off the drug to lose the tolerance. This would be especially beneficial to that group of patients whose symptoms at first appear to be benefited.

We suspect that the continued rather extensive use by physicians of the organic nitrates
in view of the development of tolerance is not due to a placebo effect of some sort, but to the intermittent use of the drug by the patient. We have seen several patients who apparently had not developed a tolerance to the blood-pressure reducing effect of the drug; and on questioning them and counting the tablets taken it was found that they had not taken any tablets for several days, but had resumed their use before visiting us. As is well known, when symptoms disappear for a few days some patients are prone to discontinue their medicine and then take it again when the symptoms return or before revisiting their physician.

Conclusions

1. The literature reveals that in the use of mannitol hexanitrate and inositol hexanitrate and other nitrates and nitrates in the management of hypertension, the possibility of the development of tolerance to the blood pressure reducing effect of these drugs has been ignored.

2. The present study in which 32 patients were alternated between periods of nitrate and placebo medication shows that tolerance to the blood-pressure reducing effects of these drugs occurred in all. The tolerance is quite well established in most subjects in eight days and well established in 14 days when a blood-pressure reducing dose of mannitol or inositol hexanitrate is given four times a day. The tolerance to these slow and prolonged acting organic nitrates is apparently completely lost in 10 days. (It may be lost in less time, but we performed no definitive tests to determine the range in an adequate number of patients.)

3. The use of organic nitrates and nitrates in the management of hypertension should be carefully individualized by determining the optimal dose for the patient and the period of tolerance and of loss of tolerance 1, 2. (Our study was not designed to compare the clinical effectiveness of the nitrates used with a placebo. To design adequately such a study, some knowledge regarding the development of tolerance to these drugs had to be obtained.)

4. In six hypertensive patients it was found that an oral dose of 0.12 Gm. of inositol hexanitrate on the average reduced the systolic pressure 44 mm. Hg and the diastolic 20 mm. Hg. The pressure had started to fall within 45 minutes, reached a maximum fall in from 60 to 150 minutes and had returned almost to the initial level in four and one half hours. Our observations on the blood-pressure reducing potency of mannitol hexanitrate as regards latent period of action, range of period of maximum fall and duration of fall confirm those in the literature7, 8. The effect of 0.25 Gm. of mannitol hexanitrate produced an effect approximately similar to that with 0.12 Gm. of inositol hexanitrate in our hypertensive patients.

SUMMARY IN INTERLINGUA

Le presente studio clinic esseva interprendite proque le litteratura clinic in re le uso de hexanitratos de mannitol e inositol—e in grande mesura etiam del alte nitritos e nitratos emplente in le tractamento de hypertesion—non se occupa del problema del disveloppamento e durantia del toleration. Nos ha constatat que toleration del action vasodilatatori de nitrato de mannitol e inositol se disveloppa intra 8 e 14 dies e se perde completely intra 10 dies post abstiner le droga. Le uso de iste nitratos deberea esser cautamente individualisate pro determinar le optime dosage e le tempore requirite pro le disveloppamento e le perdita del toleration.

REFERENCES


19 Goldberg, E.: Heart Disease, Diagnosis and Treatment. Philadelphia, Lea and Febiger, 1951.


Inositol and Mannitol Hexanitrates in Hypertension Management
LIONEL M. BERNSTEIN and A. C. IVY

Circulation. 1955;12:353-360
doi: 10.1161/01.CIR.12.3.353
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1955 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/12/3/353

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/