Nitroglycerin and Other Nitrites in the Treatment of Angina Pectoris

Comparison of Six Preparations and Four Routes of Administration

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The close chemical relationship between glyceryl trinitrate and erythrol tetranitrate suggests that these 2 drugs, despite clinical evidence to the contrary, should be equally effective in preventing attacks of angina pectoris. This proved to be true when the drugs were administered by the same route. Thus, erythrol tetranitrate when administered sublingually (instead of being swallowed, as is the custom) behaves like nitroglycerin and is one of the most effective vasodilators available. Conversely, nitroglycerin when swallowed (instead of being taken sublingually, as is the custom) is ineffective and erratic in activity. A similar striking increase in vasodilating action on sublingual administration is seen also with mannitol hexanitrate and triethanolamine trinitrate and to a lesser extent with pentaerythritol tetranitrate but not with sodium nitrite.

The prolonged effect of erythrol tetranitrate, when administered sublingually or in the buccal pouch, makes it particularly valuable in the clinical management of patients with angina pectoris.

Of all the drugs available for preventing attacks of angina pectoris nitroglycerin, amyl nitrite, and octyl nitrite are by far the most effective. Of these 3, nitroglycerin is the most widely used, primarily because of its definite dosage, simplicity of administration, and low cost. The one drawback to its clinical usefulness is the short duration of action. Measurements in this laboratory demonstrated that, although the prophylactic benefit of sublingual nitroglycerin may persist for an hour in some patients, its action persists for minutes only in most patients. Similar studies with other drugs showed that nitroglycerin is of prophylactic benefit to more patients and to a greater degree than any other medication. The present report is concerned with a search for drugs as effective as nitroglycerin, but with more prolonged activity.

The graphic chemical formulas of the 6 nitrites studied in the present series are shown in figure 1. If the action of nitroglycerin is due to the presence of -ONO₂ groups, all 6 should have therapeutic value in angina pectoris.

Two problems were of particular interest. First, since the chemical structures of nitroglycerin and erythrol tetranitrate are similar, why is the former much more effective for preventing attacks of angina pectoris? Second, since laboratory studies show that sodium nitrite has a highly effective vasodilating action, why is this drug of such limited clinical value in treating angina pectoris? A study of the extensive literature suggests that part of the difference in clinical effectiveness of these 6 drugs may be due to the various routes of administration employed.

Nitroglycerin or glycerol trinitrate is an oily liquid and, originally, was used in alcoholic solution, i.e., tincture glanoin. The vivid description by Field in 1858 showed that this solution, when dropped on the tongue, was readily absorbed by the mucous membranes of the mouth with striking effects. One of the patients treated by Field may well have suffered from angina pectoris, but Murrell is generally given credit for first advocating the
use of nitroglycerin (1879) for the treatment of this condition. Murrell prescribed 10
minims of a 1 per cent solution of nitroglycerin in water to be swallowed several times
daily. Although in the past there was some difference of opinion as to the best route of
administration, nitroglycerin has been usually prescribed for sublingual use.

Recently, a slow release preparation for oral use was made available. This material
(Nitroglyn) is a porous plastic tablet impregnated with nitroglycerin, designed so that
the drug leaches out of the matrix slowly; thus, swallowing a single tablet makes the
medication available to the patient for several hours. Few evaluations of the effectiveness
of Nitroglyn are available. Russek et al. found it of little value in correcting the exercise
electrocardiogram although Huppert and Boyd reported that its use decreased the
necessity for nitroglycerin in 16 out of 25 patients.

Nitroglycerin is readily absorbed from the skin. An ointment containing nitroglycerin
has recently been made available commercially for the treatment of peripheral vascular
disease. This preparation has been used with some clinical success in some patients with
angina pectoris.

Erythrol tetranitrate, according to the graphic formula, should be an ideal drug be-
cause it is identical with glycerol trinitrate except that its molecule is \( \frac{1}{3} \) larger; this
might well prolong its activity without detracting from its effectiveness. Bradbury's
early studies and also subsequent measurements showed that both drugs are effective
in lowering the blood pressure of laboratory animals but erythrol tetranitrate has a more
prolonged action. However, exercise tolerance and electrocardiographic measurements
showed that although erythrol tetranitrate is of some prophylactic value in some patients
with angina pectoris, it is considerably less effective than nitroglycerin, both in the degree
to which the exercise tolerance is increased and in the number of patients benefited.

One possible reason for this discrepancy might lie in the different routes of administra-
tion used with these 2 drugs. Erythrol tetranitrate is a solid and hence, unlike nitroglycerin,
is administered in tablets to be swallowed. In studying the comparative value of the differ-
ent nitrates, therefore, it is necessary to compare the effect of oral, sublingual, and paren-
teral administration.

Mannitol hexanitrate resembles glycerol trinitrate and erythrol tetranitrate in that it
is prepared by nitration of a straight chain alcohol; in this instance the alcohol contains
6 carbon atoms and the nitrate contains 6 \(-\text{ONO}_2\) groups. Mannitol hexanitrate, like
erythrol tetranitrate and the other compounds to be described, is a solid and is prescribed to
be swallowed. Studies in this laboratory indicated that mannitol hexanitrate when
given in this manner is only of moderate benefit to patients with angina pectoris.

Pentaerythritol tetranitrate like erythrol tetranitrate, has 4 \(-\text{ONO}_2\) groups; the struc-
tural configuration and physical characteristics of pentaerythritol tetranitrate, however,
are quite different from those of erythrol tetranitrate or nitroglycerin.

This drug has been the subject of a number of clinical investigations. The purely sub-
jective methods of study uniformly indicated good results but this is true of most evalua-
tions of therapy in angina pectoris, where purely subjective criteria are employed.
Several objective studies showed improvement in the exercise electrocardiogram or clinical
exercise tolerance in a high percentage of patients. \textsuperscript{10, 29-33} In other instances \textsuperscript{6, 34-36} similar objective studies gave less favorable results. Winsor and Scott\textsuperscript{33} found the drug to be effective when administered sublingually.

Triethanolamine trinitrate biphosphate, like nitroglycerin, has 3 -ONO\textsubscript{2} groups; the structural configuration, however, resembles pentaerythritol tetranitrate rather than nitroglycerin.

This nitrite was introduced following favorable reports from Europe.\textsuperscript{37-39} Experiments on the isolated rabbit heart demonstrated coronary vasodilatation.\textsuperscript{40} Several clinical evaluations reported favorable subjective results.\textsuperscript{41-43} However, poor results have been reported by one group of workers, who also evaluated the drug by clinical observation,\textsuperscript{44} and by another group,\textsuperscript{10} who evaluated the drug by electrocardiographic measurements after exercise and compared the results with those following other preparations including pentaerythritol tetranitrate and Nitroglyn.

Sodium nitrite is the simplest nitrite available. Studies in laboratory animals\textsuperscript{45} indicated that it is a highly effective coronary vasodilator but it has proved ineffective when given in 60 mg. doses to patients with angina pectoris.\textsuperscript{1} In laboratory studies the drug is given parenterally and in doses (considering the weight of the subjects) considerably larger than those given orally to human subjects.

**Methods**

The methods of study have been described in detail elsewhere.\textsuperscript{4, 5, 46} In brief, they involved the following steps:

*Subjects*

A group of typical patients with angina pectoris were observed for many weeks, both without treatment and while taking placebos, in order to evaluate the severity and relative constancy of symptoms.

The 34 subjects of the present study included 20 men and 14 women. All but 2 patients were 51 years of age or older. In each instance the angina pectoris was due to coronary artery disease. These 34 patients were similar to other groups previously studied in this laboratory except for a higher percentage of women and a higher percentage of patients who responded favorably to nitroglycerin.

**Methods of Observation.** At weekly intervals, for many months, the clinical response to therapy was evaluated by 2 physicians while another physician independently measured the amount of exercise necessary to induce angina under standardized conditions. The standardized conditions of the exercise tolerance test are important.\textsuperscript{4, 6-7} They involve repeated trips over a 2-step staircase in a relatively cold environment (45 to 55 F.) until an attack of angina, typical for that patient, is precipitated.

**Medication.** The 6 nitrites were administered in at least 21 different shapes, colors, vehicles, or concentrations. Placebos in at least 10 different forms were also administered.

The first medication prescribed was invariably a placebo. Thereafter, there was no uniform order except that each beneficial response was followed by a placebo and later by re-administration of the apparently effective medication in disguised form. As a result of these precautions, neither the patient nor the observer who measured the standardized exercise tolerance could recognize the medication. Thus, the conditions of the "double-blind test" were fulfilled.

**Routes of Administration, Dosage and Time of Measurements**

The 6 nitrites were given sublingually (or buccally), subcutaneously (or intramuscularly), by mouth (to be swallowed), and by inunction. The doses employed were those recommended by the manufacturer as adequate and several times larger if the recommended dose proved inadequate. Except when given parenterally, the medication was taken several times daily for at least 1 week before the response was measured. The Standardized Exercise Tolerance was measured at a time appropriate for demonstrating the effect of the morning dose.

**Sublingual or Buccal Therapy.** Medication was taken 3 times daily after meals. The Standardized Exercise Tolerance Test was performed 2 minutes after an 0.3 mg. "hypodermic tablet" of nitroglycerin had dissolved under the patient's tongue; in most instances from 20 to 30 seconds were required for complete solution of the tablet.

Since the only available preparations of the other 5 nitrites were meant to be swallowed, these tablets were used for the sublingual or buccal pouch studies also. The exercise tolerance was measured within 20 minutes after these tablets had dissolved except when the duration of action was studied. The erythrol tetranitrate was obtained from 3 sources. The tablets contained 15 mg. of erythrol tetranitrate when prepared. Some deterioration must have taken place because freshly opened bottles gave off a distinct odor of nitric acid and the cotton wadding in 1 preparation had disinte-
NITRITES IN THE TREATMENT OF ANGINA PECTORIS

grated to powder. Two of the preparations (those marketed by Burroughs Wellcome Co. and Merck and Co.) usually required from 1 to 1 ½ hours in contact with the oral mucosa for disintegration; the latter product is no longer available commercially. The third preparation (a Merck product, marketed by Sharpe and Dohme Co.) disintegrated more rapidly, usually in ½ to 1 hour, and contained 15 mg. of active drug in a 230-mg. tablet.

The mannitol hexanitrate contained 32.5 mg. of the drug in a tablet weighing 494 mg. These tablets were quite large. They dissolved or disintegrated sublingually in about 15 minutes. The dose used was 65 mg. 3 times daily.

Two preparations, each containing 2 mg. of triethanolamine trinitrate biphosphate (Metamine) were used in doses of 1 to 4 tablets 3 times daily.

Pentaerythritol tetranitrate (Peritrate) was obtained from 2 sources* as tablets of 10 or 20 mg. The doses were usually 40 to 50 mg. 3 times a day; several subjects also received 10 mg., 3 times a day. The exercise tolerance tests were performed within ½ hour after sublingual solution of the tablets.

In most instances, the dose of sodium nitrite was 0.3 Gm. (5 tablets). Patients who experienced faintness with this dose were given smaller doses but usually had similar untoward reactions with as little as 60 mg.

Parenteral Administration. The Standardized Exercise Tolerance Test was performed 20 minutes to ½ hour after a single injection of medication. During the preceding week these patients had taken placebos by mouth, 3 times daily.

Nitroglycerin was given subcutaneously in doses of 0.3 mg.

Erythrol tetranitrate used for subcutaneous administration was obtained by extraction of the active principle from the tablets with alcohol and ether. This extract was then mixed with lactose, made into hypodermic tablets, and assayed for potency. Erythrol tetranitrate is only slightly soluble in water, so that much of the 15 mg. dose was probably in suspension when injected hypodermically.

The solution of triethanolamine trinitrate biphosphate for parenteral administration was supplied by the manufacturer. The dose employed was 4 mg., administered intramuscularly. Unfortunately, its use was followed by considerable, although temporary, local pain, which may have decreased its efficacy.

Sodium nitrite was administered intramuscularly in doses of 0.06 to 0.18 Gm.

Mannitol hexanitrate and pentaerythritol tetranitrate were not given parenterally.

Oral or Swallowed Medication. Nitroglycerin was given twice daily, all others 3 times daily (on arising, at 2:00 to 3:00 p.m., and on retiring) for 1 week and the Standardized Exercise Tolerance Test was performed from 1 to 2 hours after the last morning dose.

Nitroglycerin was given in 2 forms. In order to prevent absorption from the oral mucous membranes, hypodermic nitroglycerin tablets were en-cased in gelatin capsules before being swallowed. The minimum dose used in these studies was 0.45 mg. t.i.d. In order to determine the effective dose of nitroglycerin when swallowed, doses of 1 to 15 mg. (in capsules containing 1 mg. or 3 mg. each) were given to 13 patients. Studies with Nitrogly were also carried out with varying doses.

Erythrol tetranitrate was administered in doses of 30 mg. 3 times daily for at least 1 week.

Mannitol hexanitrate was given in doses of 65 mg.

After preliminary studies with 2 mg. tablets, the dosage of triethanolamine trinitrate biphosphate used was 6 mg., 3 times daily for at least a week.

The dosage of pentaerythritol tetranitrate used was 40 to 50 mg. 3 times a day; several subjects also took 10 mg. 3 times a day.

Twenty-nine patients were requested to take 300 mg. of sodium nitrite 3 times daily for 1 week. Patients who developed untoward effects to this dose were given smaller doses.

Inunction. These studies were carried out with nitroglycerin and erythrol tetranitrate ointments.

Four inches of Nitrol Ointment (containing approximately 43 mg. of nitroglycerin) were rubbed in well twice daily for 1 week. The Standardized Exercise Tolerance Test was performed approximately 2 hours after the last dose.

The erythrol tetranitrate material for inunction was made by incorporating the specially prepared hypodermic tablets in a water soluble ointment base. An amount containing approximately 65 mg. of erythrol tetranitrate was rubbed in well, morning and night for 1 week and the exercise test carried out 2 hours after the last application.

Analysis of Results

The results were evaluated by studying the patient’s record of the number of attacks experienced during each period of therapy; by asking the patient’s opinion of the effectiveness of the treatment; and, most important, by measurement of the patient’s exercise tolerance under the standardized conditions of the test. The following degrees of response were recognized.

Marked response. The patient was able to perform at least 25 per cent more work without angina than when taking placebos and stopped exercise because of dyspnea or fatigue, rather

*Malbie Laboratories and Warner Chilcott Co.
than pain; or angina was induced but only after a 50 per cent increase in exercise above the level with placebos.

Moderate Response. Angina did not occur but the increased work was no more than 24 per cent; or angina was induced after an improvement of exercise tolerance of 20 to 49 per cent.

Slight response. This implied a 10 to 19 per cent increase in exercise tolerance before angina was precipitated.

No response. Angina was induced after no more exercise than the maximum that could be performed during the placebo period. A decrease in exercise tolerance was not infrequent in these cases. In such instances the medication failed to improve the patient's condition sufficiently to overcome the deleterious effects of factors that increase the tendency to attacks (emotion, intercurrent illness, etc.). This apparent decrease in exercise tolerance does not imply that the clinical condition was made worse; it must be remembered that the change in exercise tolerance was determined by comparison with the maximum amount of work that the patient could perform while taking placebos.

All positive and many negative results were checked by re-administering the drug at a later date in disguised form or by comparison with the response to larger doses, except in a few instances where a change in the patient's condition (complete remission of symptoms, progression of disease, unavailability of the patient, etc.) prevented repetition.

As in previous studies6, 7, 8, 9-20 the patients were divided into 3 groups according to the increase in their exercise tolerance 2 minutes after the solution sublingually of 0.3 mg. nitroglycerin.

Group 1 included those patients who had a "marked response" to sublingual nitroglycerin.

Group 2 patients had a "moderate response" to sublingual nitroglycerin.

Group 3 patients showed "slight response" or "no response" to sublingual nitroglycerin.

Electrocardiographic Studies.

These were carried out in a few patients to demonstrate coronary vasodilator activity according to methods previously described.6, 7, 8, 9-21 Coronary vasodilatation was indicated by prevention of S-T depression in lead 4R after the same amount of work that caused definite S-T depression plus an attack of angina pectoris when the patient was taking placebos.

RESULTS

The results are presented in tables 1 and 2. As in previous studies2-5, 47, 50, 52 the 20 group 1 subjects were far more likely to respond to other medication than were the 5 group 2 or the 9 group 3 patients. Comparison of the effects of medication, therefore, is best observed in group 1 subjects (fig. 2).

Nitroglycerin

Sublingual Administration. The dosage used caused no untoward effects in the 34 subjects. Thirteen of the 20 group 1 patients were able to exercise until fatigued without developing angina. The remaining 7 were able to increase their exercise tolerance by 62 to 135 per cent before they developed angina.

Subcutaneous Administration. In 7 of the 10 group 1 subjects, the degree of beneficial response was comparable to that following sublingual administration of the same dose.

Oral Administration. Thirteen of the 15 group 1 subjects who swallowed capsules containing 0.45 mg. of nitroglycerin showed no significant response while only 2 showed "moderate" increases in exercise tolerance.

The swallowed dose of nitroglycerin necessary to increase the ability to exercise is shown in table 3. In 11 group 1 subjects, a "marked response" required a minimum of 2 or 3 mg. in 3 patients, 5 or 6 mg. in 2 patients, and 15 mg. in 2 patients. Two other patients showed a moderate response to 2 or 4 mg. but did not receive larger doses. The remaining 2 subjects failed to show a response after 15 mg. There were no untoward effects.

Fourteen group 1 subjects received Nitroglycerin (table 3). Six showed a "marked response";1, after 1 tablet (6 mg.); 2, following 12 mg.; 3 required 18, 24, and 30 mg., respectively. Two additional patients showed a "moderate response" after 12 and 24 mg., respectively. Two patients showed no response to as much as 30 mg. The remaining 4 showed no response after 12 mg., but received no larger doses.

Administration by Inunction (table 4). One of 6 group 1 patients showed a "marked response" to Nitrol Ointment and 3 others showed responses that were "moderate" but appreciably less than followed sublingual nitroglycerin in the same patients.
## Table 1: Comparative Efficacy of Six Nitrates Administered Sublingually, Subcutaneously, and by Swallowing

<table>
<thead>
<tr>
<th>Patient</th>
<th>Nitroglycerin</th>
<th>Erythrol tetranitrate</th>
<th>Mannitol nitrate</th>
<th>Sodium nitrite</th>
<th>Potassium-ethylxanthate</th>
<th>Theobromine trihydrate</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Expectorated</td>
<td>Expectorated</td>
<td>Expectorated</td>
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<td>30-40</td>
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<td>30-40</td>
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</table>

* Nitrates were administered sublingually, subcutaneously, and by swallowing. * A decrease in exercise tolerance as compared with the maximum amount spontaneously intramuscularly. * P.O.: Medication administered by mouth. * No attack of angina pectoris induced.


**Table Notes:**
- Nitrates were administered in six groups:
  - Group 1: Nitroglycerin
  - Group 2: Erythrol tetranitrate
  - Group 3: Mannitol nitrate
  - Group 4: Sodium nitrite
  - Group 5: Potassium-ethylxanthate
  - Group 6: Theobromine trihydrate

- Exercise tolerance was measured using the S.P.E.T. test.
- Results were compared between groups to assess efficacy.

**Exercise Tolerance:**
- 60 seconds: Maximum exercise tolerance, as compared with the maximum amount spontaneously intramuscularly.
- P.O.: Medication administered by mouth.

**Untoward Effects:**
- No attack of angina pectoris induced.
- Medication followed by untoward effect.

**Patient Information:**
- Gender: Male (M) and Female (F)
- Age range: 30-40 years
- Initial symptoms and responses to nitrates were recorded.
# Table 2—Summary—Comparative Efficacy of Six Nitrites Administered Sublingually, Parenterally, and by Swallowing

<table>
<thead>
<tr>
<th>Nitroglycerin</th>
<th>Erythrol tetranitrate</th>
<th>Mannitol hexanitrate</th>
<th>Triethanolamine trinitrate biphosphate</th>
<th>Pentru-erythritol tetranitrate</th>
<th>Sodium nitrite</th>
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<td>8</td>
<td>8</td>
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</tbody>
</table>

S.L., Medication administered sublingually or in the buccal pouch; S.Q., Medication administered subcutaneously or intramuscularly; P.O., Medication administered by mouth.
Erythrol Tetranitrate

Sublingual or Buccal Administration. In the 20 group 1 patients the magnitude of the response to 15 mg. was comparable to that following nitroglycerin in 9 subjects, somewhat less, but of considerable benefit in 8, and of little value in the remaining 3 patients. In accordance with previous studies, the clinical response during the weeks of administration was uniformly excellent in those patients who showed a "marked" or a "moderate response."

Patients did not object to sublingual or buccal use of the drug during the comparatively short period of study. Severe pounding headache similar to that experienced by some patients after nitroglycerin was reported by 2 of the total 34 patients. This was relieved by aspirin. More severe headache, sufficient to cause the patient to discontinue the medication, was reported by 4 patients who took 2 tablets (30 mg.).

The beneficial action of the drug did not become evident until 6 to 10 minutes after the drug was placed under the tongue. The duration of action persisted for at least 1 to 2 hours after dissolution of the tablet (table 5).

Subcutaneous Administration. Five out of 7 group 1 patients responded to parenteral injection but the increase in exercise tolerance was somewhat less than what followed sublingual administration.

Oral Administration. Swallowing 30 mg. of erythrol tetranitrate was distinctly less beneficial than sublingual or subcutaneous administration of 15 mg. (table 2).

Administration by Inunction. The results were similar to those obtained with nitroglycerin ointment in 6 of the 7 patients studied (table 4).

Maninitol Hexanitrate

Here again the nitrite was comparatively ineffective when swallowed but highly effective when given by the sublingual route. There were no untoward effects.

Triethanolamine Trinitrate Biphosphatate

Sublingual Administration. Of 12 group 1 subjects, 2 showed a "marked response," 3 a "moderate response," 4 "no response," and 3 discontinued the therapy because of painful sublingual stomatitis. One additional patient (who showed a "moderate response") had a similar stomatitis but continued therapy. In general, the increase in exercise tolerance was less than after sublingual erythrol tetranitrate or nitroglycerin.

Oral Administration. All 21 patients who swallowed 6 mg. of Metamine 3 times a day for at least 1 week showed "no response." There were no headaches or other untoward effects.

Parenteral Administration. One out of 5 group 1 patients had a "moderate response."

Pentaerythritol Tetranitrate

This drug was not administered parenterally or by inunction.

Sublingual Administration. Two out of 15 group 1 subjects showed a "marked response," and 6 a "moderate response." There were no untoward reactions. In general the magnitude of the response was less than that following nitroglycerin, but somewhat greater than when pentaerythritol tetranitrate was swallowed.

Oral Administration. Out of 17 group 1 patients 1 showed a "marked response," and 4 a "moderate response." There were no untoward reactions.

Sodium Nitrite

The route of administration did not affect the results as strikingly as with other preparations used in this study, but untoward effects were frequent and related to peripheral rather than intracranial dilatation.

Sublingual Administration. This was employed in 16 group 1 patients. No patient had a "marked response," while 4 had a "moderate response." Four patients omitted the drug because of faintness; 1 additional patient continued the drug despite faintness and showed no therapeutic response.

Subcutaneous Administration. One of the 6 group 1 subjects had a "marked response," 2
<table>
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<td>Usual S.E.T.T. trips</td>
<td>“ Hypo. ” tablets</td>
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<td></td>
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<td>(dose in mg.)</td>
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<tr>
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<td>M</td>
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<td>24-28</td>
<td>142†</td>
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<td>I.K.</td>
<td>M</td>
<td>63</td>
<td>16-23</td>
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<tr>
<td>M.Ke.</td>
<td>F</td>
<td>60</td>
<td>25-30</td>
<td>120†</td>
</tr>
<tr>
<td>M.R.</td>
<td>M</td>
<td>51</td>
<td>29-34</td>
<td>106†</td>
</tr>
<tr>
<td>E.W.</td>
<td>F</td>
<td>65</td>
<td>19-23</td>
<td>93</td>
</tr>
<tr>
<td>M.Ko.</td>
<td>M</td>
<td>53</td>
<td>36-44</td>
<td>89</td>
</tr>
<tr>
<td>S.C.</td>
<td>F</td>
<td>63</td>
<td>22-26</td>
<td>81†</td>
</tr>
<tr>
<td>F.D.</td>
<td>F</td>
<td>50</td>
<td>26-30</td>
<td>76</td>
</tr>
<tr>
<td>R.Sh.</td>
<td>F</td>
<td>41</td>
<td>45-60</td>
<td>67†</td>
</tr>
<tr>
<td>M.B.</td>
<td>M</td>
<td>74</td>
<td>29-33</td>
<td>67†</td>
</tr>
<tr>
<td>R.L.</td>
<td>M</td>
<td>63</td>
<td>20-26</td>
<td>62</td>
</tr>
<tr>
<td>T.K.</td>
<td>M</td>
<td>51</td>
<td>68-75</td>
<td>60†</td>
</tr>
<tr>
<td>A.T.</td>
<td>F</td>
<td>64</td>
<td>18-27</td>
<td>48†</td>
</tr>
<tr>
<td>M.F.</td>
<td>M</td>
<td>69</td>
<td>54-76</td>
<td>45†</td>
</tr>
<tr>
<td>A.C.</td>
<td>M</td>
<td>68</td>
<td>26-36</td>
<td>44†</td>
</tr>
<tr>
<td>H.S.</td>
<td>M</td>
<td>53</td>
<td>65-70</td>
<td>42†</td>
</tr>
<tr>
<td>M.D.</td>
<td>M</td>
<td>58</td>
<td>30-37</td>
<td>35†</td>
</tr>
<tr>
<td>T.Me.</td>
<td>M</td>
<td>65</td>
<td>33-36</td>
<td>6</td>
</tr>
<tr>
<td>A.Z.</td>
<td>M</td>
<td>58</td>
<td>20-24</td>
<td>0</td>
</tr>
<tr>
<td>F.B.</td>
<td>F</td>
<td>54</td>
<td>30-34</td>
<td>-12</td>
</tr>
</tbody>
</table>

S.E.T.T., Standard Exercise Tolerance Test. S.L., Medication administered sublingually.

* Medication followed by headache.
† No attack of angina pectoris induced.

- A decrease in exercise tolerance compared with the maximum amount that could be performed during the placebo trial.
NITRITES IN THE TREATMENT OF ANGINA PECTORIS

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TABLE 4.—Comparative Effect of Nitrates Given Sublingually and by Inunction

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age</th>
<th>Placebos (orally) S.E.T.T. trips</th>
<th>Increase in exercise tolerance (per cent)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Nitroglycerin S.L.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Nitroglycerin</td>
</tr>
<tr>
<td>H.N.</td>
<td>M</td>
<td>67</td>
<td>24-28</td>
<td>142†</td>
</tr>
<tr>
<td>I.K.</td>
<td>M</td>
<td>63</td>
<td>16-23</td>
<td>135</td>
</tr>
<tr>
<td>M.R.</td>
<td>M</td>
<td>51</td>
<td>29-34</td>
<td>106†</td>
</tr>
<tr>
<td>E.W.</td>
<td>F</td>
<td>65</td>
<td>19-23</td>
<td>93</td>
</tr>
<tr>
<td>F.D.</td>
<td>F</td>
<td>50</td>
<td>26-30</td>
<td>76</td>
</tr>
<tr>
<td>M.F.</td>
<td>M</td>
<td>69</td>
<td>54-76</td>
<td>45†</td>
</tr>
</tbody>
</table>

Group 1

S.E.T.T., Standardized Exercise Tolerance Test; S.L., Medication administered sublingually.
†No attack of angina pectoris induced.
- A decrease in exercise tolerance as compared with the maximum amount that could be performed during the placebo trial.

TABLE 5.—Speed of Onset and Duration of Action of Erythrol Tetranitrate Administered Sublingually to Group 1 Subjects

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age</th>
<th>S.E.T.T. minutes after sublingual administration of erythrol tetranitrate (per cent)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Immediate</td>
</tr>
<tr>
<td>H.N.</td>
<td>M</td>
<td>67</td>
<td>24-28</td>
</tr>
<tr>
<td>I.K.</td>
<td>M</td>
<td>63</td>
<td>16-23</td>
</tr>
<tr>
<td>M.Ke.</td>
<td>F</td>
<td>60</td>
<td>25-30</td>
</tr>
<tr>
<td>M.R.</td>
<td>M</td>
<td>51</td>
<td>29-34</td>
</tr>
<tr>
<td>E.W.</td>
<td>F</td>
<td>65</td>
<td>19-35</td>
</tr>
<tr>
<td>M.B.</td>
<td>M</td>
<td>74</td>
<td>29-33</td>
</tr>
<tr>
<td>A.T.</td>
<td>F</td>
<td>64</td>
<td>18-27</td>
</tr>
</tbody>
</table>

S.E.T.T., Standard Exercise Tolerance; S.E.T.T., Standardized Exercise Tolerance Test.
†No attack of angina pectoris induced.
- A decrease in exercise tolerance compared with the maximum amount that could be performed during the placebo trial.

showed “moderate response,” and 1 was not exercised because of faintness. Five subjects who had untoward reactions when given the drug by other routes did not receive it parenterally.

Oral Administration. Of 18 group 1 subjects who swallowed this drug 2 showed a “marked response,” and 3 a “moderate response.” Three discontinued the drug because of faintness, pallor, and sweating. Doses of 180 mg. and 60 mg. caused similar but less severe reactions, accompanied by a fall in blood pressure in these 3 patients, even when the 60-mg. tablet was disguised. One additional patient noted faintness but continued the drug.

Electrocardiographic Studies

Electrocardiographic studies before and after exercise were carried out in 8 subjects (4 in group 1, 1 in group 2, 3 in group 3), following the administration of placebos, nitroglycerin sublingually, and both erythrol
tetranitrate and triethanolamine trinitrate biphosphate administered sublingually and by swallowing (table 6).

The S-T depression in lead 4R after exercise was appreciably less in 6 out of 7 subjects who received nitroglycerin sublingually, in all 4 subjects who received erythrol tetranitrate sublingually, in 3 out of 5 who received this drug by mouth, in 2 out of 4 who received Metamine sublingually, and in 2 out of 4 who took this drug by mouth.

**DISCUSSION**

In this study, as in previous studies, a "marked response" or a "moderate response" to medication as measured by the Standardized Exercise Tolerance Test, was of clinical significance. Patients who showed this degree of response experienced no attacks or almost no attacks in daily life while taking the medication, and such results were reproduced even when the medication was disguised. In contrast, a "slight response" to medication was of no clinical significance and any apparent clinical improvement was fortuitous or due to the patient's faith in therapy and was not likely to be persistent or reproducible. Since group 1 subjects (those who show a "marked response" to nitroglycerin administered sublingually) are the ones most likely to respond to other effective medication, study of this group makes it possible to compare the effectiveness of medication with a minimum of confusing data (fig. 2).

Not only do patients differ greatly in their response to treatment, but drugs also differ considerably in their effectiveness in preventing attacks of angina pectoris. In accord with previous studies, therapeutic measures can be divided into 3 groups. Group A includes drugs that are highly effective both clinically and by exercise tolerance studies in a large number of patients, especially group 1 subjects (those responding to sublingual nitroglycerin). Group B includes drugs of only moderate value in such subjects. Group C drugs are of little or no value.

**Nitroglycerin.** When administered sublingually, nitroglycerin is the most effective of all group A drugs in common use. Not only do more patients show a response to this form of treatment, but the degree of response (i.e., the amount by which the patients' exercise tolerance can be increased before angina is induced) is greater than is observed after any other medication. Because of its short dura-

---

**Table 6.—Effect of Medication on the Degree of S-T Depression Induced by Exercise**

<table>
<thead>
<tr>
<th>Subject</th>
<th>Placebo S.L. or P.O.</th>
<th>Nitroglycerin S.L.</th>
<th>Erythrol tetranitrate S.L.</th>
<th>Triethanolamine trinitrate biphosphate S.L.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of trips</td>
<td>S-T depression* (mm.)</td>
<td>Number of trips</td>
<td>S-T depression* (mm.)</td>
</tr>
<tr>
<td>Group 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H.N.</td>
<td>28</td>
<td>0.8</td>
<td>28</td>
<td>0.0</td>
</tr>
<tr>
<td>M.B.</td>
<td>33</td>
<td>0.95</td>
<td>33†</td>
<td>0.15</td>
</tr>
<tr>
<td>A.T.</td>
<td>27</td>
<td>2.5</td>
<td>27†</td>
<td>1.45</td>
</tr>
<tr>
<td>M.P.</td>
<td>32</td>
<td>0.85</td>
<td>32†</td>
<td>0.0</td>
</tr>
<tr>
<td>Group 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E.R.</td>
<td>20</td>
<td>1.6</td>
<td>20†</td>
<td>0.45</td>
</tr>
<tr>
<td>Group 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T.Me.</td>
<td>30</td>
<td>6.4</td>
<td>30†</td>
<td>3.25</td>
</tr>
<tr>
<td>A.Z.</td>
<td>22</td>
<td>0.95</td>
<td>22</td>
<td>0.15</td>
</tr>
<tr>
<td>F.B.</td>
<td>30</td>
<td>0.95</td>
<td>30†</td>
<td>1.0</td>
</tr>
</tbody>
</table>

S.L., Medication administered sublingually or in buccal pouch; P.O., Medication administered by mouth.

* Average of 10 consecutive complexes.

† No attack of angina pectoris induced.

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tion of action, the prophylactic use of this drug is usually limited to administration immediately before undertaking any task.

Nitroglycerin administered by mouth, on the other hand, is a group C drug and is of little clinical value to most patients in the doses usually employed. To be effective when swallowed, a single dose of nitroglycerin must be many times larger than the usual sublingual one (table 3). The reasons for this marked difference in effectiveness is not known. The equal effectiveness of nitroglycerin given subcutaneously and sublingually suggests that the drug is inactivated in the gastrointestinal tract. Hypodermic administration of nitroglycerin has limited value in clinical practice because of the inconvenience of self-medication; it might be of value in the treatment of acute exacerbations of the disease, but sublingual administration is as effective and simpler to use.

The results with Nitroglyn, a pharmaceutical preparation of nitroglycerin intended for oral use, are in accord with these findings. Nitroglyn is a group B drug. It was of marked or moderate value in 57 per cent of 14 group 1 patients, but only in doses that were 2 to 4 times larger than that advocated by the manufacturer and many times larger than originally advised. At least part of the lack of objective evidence of the usefulness of nitroglycerin when given by mouth may be due to the short duration of action, if so, it limits further the clinical value of this form of treatment.

The effectiveness of nitroglycerin by injection (group B) is of interest because it illustrates the well-known fact that this drug can be absorbed through the unbroken skin. This characteristic is responsible for the headaches of workers manufacturing dynamite. The lack of popularity of treatment by injection further limits its value in present day clinical therapy of angina pectoris.

**Erythrol Tetranitrate.** According to the present and previous studies in this laboratory\(^1\),\(^2\) erythrol tetranitrate, when swallowed, is a group B therapeutic agent, i.e., it is effective to a moderate degree in a small percentage of patients. In marked contrast, however, are the results of the present investigation that erythrol tetranitrate, given sublingually, is one of the most highly effective group A agents. The frequency of this beneficial action and the degree of increase in exercise tolerance

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**Fig. 2.** Frequency of moderate or marked response of group 1 subjects to 6 nitrites administered sublingually, subcutaneously, and when swallowed.
after sublingual erythrol tetrani-trate approximate the effects of nitroglycerin, amyl nitrite, and octyl nitrite more closely than do any other of the approximately 100 preparations tested in this laboratory. Furthermore, the duration of this beneficial action is prolonged sufficiently to make this method of treatment of practical clinical value. On the other hand, the speed of onset of action is too slow to permit its use for the treatment of individual attacks. Further studies of the speed of onset and duration of action are advisable with tablets especially prepared for sublingual or buccal use, but the solubility of erythrol tetrani-trate in water is much less than that of nitroglycerin and it is unlikely that it can replace the latter drug for the treatment of individual attacks. The slow disintegration time of the available tablets may be of some added value in prolonging the duration of action. The absence of local discomfort makes it possible to retain the tablet in the buccal pouch for prolonged periods without interfering with normal activity (including speech); for obvious convenience, it is probably advisable to use the drug after meals.

With the doses used (15 mg. t.i.d.) headache was infrequent; with larger doses (30 mg.) severe pulsating headache was often troublesome. This is probably due to intracranial vasodilatation and is additional evidence of the drug's activity; it is seen frequently with large doses of the active nitrates such as nitroglycerin, amyl nitrite, and octyl nitrite\(^5\) as well as with erythrol tetrani-trate, but it is not seen with the other weaker nitrates used in this study, nor with other weak vasodilators such as the purines and the cinchona alkaloids.\(^1\)\(^,\)\(^6\)\(^,\)\(^52\)

The beneficial results of erythrol tetrani-trate when given subcutaneously or by immersion are additional evidence of its absorption parenterally and from the skin respectively. This action is probably of limited clinical application.

**Mannitol Hexanitrate.** It is evident from the present as well as previous exercise tolerance studies\(^2\)\(^,\)\(^21\) that this is a group B drug when swallowed in doses of 65 mg. 3 times daily. In contrast, although the number of subjects in the present series is small, it is evident that mannitol hexanitrate is a group A drug when administered sublingually.

The practical clinical value of this therapeutic procedure is decreased considerably by the size of the tablets available on the market. The commercially available tablets are large because the Bureau of Explosives has advised that mannitol hexanitrate be diluted with at least 10 parts of inert material to assure safety in transportation. This degree of dilution may not be essential, however, for although the American preparation of its close relative, erythrol tetrani-trate (Merck) also is marketed in a dilution of 1:15, the British preparation (Burroughs Wellcome) has been marketed for years in approximately a 1:2 dilution.

It is evident that as the number of carbon atoms in the chain, or as the size of the molecule is increased, the vasodilator activity is decreased even though the number of -ONO\(_2\) groups may be increased. Thus the effective sublingual dosages for nitroglycerin, erythrol tetrani-trate, and mannitol hexanitrate is 0.3, 15, and 65 mg., respectively, while the effective sublingual doses for Peritrate and Metamine are considerably larger than that of nitroglycerin.

**Triethanolamine Trinitrate Biphosphate (Metamine).** Here again the drug was much more effective when given sublingually or by injection than when given by mouth. Headache was not experienced; this suggests that its vasodilating action is comparatively weak. Other untoward effects, however, (e.g., stomatitis when given sublingually and pain when given intramuscularly) limit its usefulness by these more effective routes.

**Pentaerythritol Tetrani-trate.** This drug is of definite but moderate value in a small percentage of patients. It is classified, therefore, as a group B drug. There was no great difference in the frequency or degree of its effectiveness by the sublingual or by the oral route. This is in accordance with the fact that it is not readily absorbed from the skin or gastro-
intestinal tract, and also with the report that munitions workers who handle the chemical do not develop the typical nitrite headache.

The frequency of beneficial results with pentaerythritol tetranitrate in the subjects of the present series would seem to be less than that demonstrated by the objective electrocardiographic studies of Russek et al. This difference, however, is probably not as great as would appear, because Russek’s subjects were limited to those whose electrocardiographic changes following exercise could be prevented by the administration of nitroglycerin. It would appear, therefore, that Russek’s subjects corresponded to the more susceptible group 1 patients of the present series and such patients are likely to respond to pentaerythritol tetranitrate.

Sodium Nitrite. The discrepancy between the striking responses reported in animal experiments where the drug was given parenterally and the comparative ineffectiveness of the drug when given orally to patients with angina pectoris is probably due at least in part to the different routes of administration employed in these 2 studies and in part to the much smaller doses usually given clinically.

It is evident that larger doses (300 mg. t.i.d.) are much more effective than the 60 mg. doses usually employed in men. The drug is equally effective when absorbed from either the buccal mucosa or the gastrointestinal tract, but it is more effective when given parenterally. The frequency of effectiveness parenterally would probably have been greater in the present series if it had been administered to the 5 additional patients who developed untoward reactions when taking the drug sublingually or by mouth. The untoward reactions from this drug are quite different from, and more frequent than, those seen following the other nitrites. Headache was not encountered but hypotensive reactions occurred in over one third of the group 1 patients. This further limits the clinical usefulness of the drug in the treatment of angina pectoris.

Electrocardiographic Studies. Nitroglycerin, erythrol tetranitrate, and Metamine in the present series and with pentaerythritol tetranitrate in other series yielding objective electrocardiographic evidence of a true pharmacodynamic activity indicating that they prevent or diminish myocardial anoxia, presumably by coronary vasodilatation. Such electrocardiographic studies cannot be accepted as evidence of therapeutic efficiency, however, for the following reasons: 1. There is no constant relationship between the occurrence of the electrocardiographic changes and the occurrence of cardiac pain. 2. Only a small percentage of angina patients are suitable for such studies. Thus, although electrocardiographic studies after exercise or anoxemia demonstrate a pharmacologic effect, they yield no information concerning the frequency of beneficial clinical effect in the preponderant percentage of patients who are not suitable for such electrocardiographic studies. 3. Technical difficulties make it difficult to reproduce identical results on repeated tests. This is especially true in patients with angina pectoris because the electrocardiogram at rest may show varying degrees of S-T depression spontaneously on different days.

Untoward Effects. The occurrence of headache with nitrate therapy has been discussed. It is of short duration and can be avoided by decreasing the dose or can be treated with aspirin. The possibility of other untoward effects with prolonged use of the nitrites, although unlikely, must be kept in mind.

Early reports suggested the possibility of methemoglobinemia because of cyanosis or a brown discoloration of the blood. Early spectrophotometric methods, although more specific than these clinical observations, were subject to inaccuracies and inconsistencies. Modern hemoglobin spectrophotometry, which permits precise diagnosis, has shown methemoglobinemia in cases of sodium nitrite poisoning, but it has been pointed out that this is unlikely with therapeutic doses.

Angina pectoris and even cardiac deaths have been encountered in young munitions
workers who manufacture dynamite from
nitroglycerin. This may be due to reactive
vasoconstriction that may occur when the drug
is withdrawn abruptly after prolonged expos-
ure to large doses. The necessity for indus-
trial safeguards for munitions and pharma-
tical workers who have prolonged or frequent
exposure to nitrites has been stressed. This
type of withdrawal reaction has not been re-
ported following therapeutic doses.

Hypotension, cardiovascular collapse, and
myocardial infarction have been reported fol-
lowing nitroglycerin or octyl nitrite, especially in patients consuming significant
amounts of alcohol while taking nitrites. Such reactions are readily avoided by adjust-
ing the dosage and especially by avoiding over-
dosage such as may occur if the rapidly acting
nitrites are administered repeatedly with only a few minutes between doses.

**SUMMARY**

The comparative value of 6 different nitrites
in the treatment of angina pectoris when ad-
ministered by the oral, sublingual, subcu-
taneous, and percutaneous routes was studied in
34 patients by measuring the amount of work
that could be performed under standardized
conditions without inducing angina and also
by observing the clinical response and the
exercise electrocardiogram.

Glycerol trinitrate, erythrol tetranitrate,
mannitol hexanitrate, and triethanolamine-
trinitrate biphosphate were all much more
effective sublingually than when swallowed.

Nitroglycerin and erythrol tetranitrate
when administered sublingually are among
the most effective of all prophylactic agents
available for the treatment of patients with
angina pectoris. The comparatively prolonged
duration of action of erythrol tetranitrate
when given sublingually makes it especially
valuable for clinical use.

Nitroglycerin and erythrol tetranitrate were
also effective when administered parenterally
or by inunction but their value was markedly
limited when swallowed. This suggests that
these nitrites are inactivated in the gastroin-
testinal tract. Mannitol hexanitrate also was

more effective sublingually than when swal-
lowed but was of limited clinical value because
of the large size of the tablets available. Tri-
ethanolamine trinitrate was moderately effec-
tive when administered sublingually but of no
demonstrable value when swallowed. Sub-
lingual therapy with this drug is limited be-
cause of the frequent glossitis that follows its
use.

Pentaerythritol tetranitrate showed little
difference in the frequency of response when
administered sublingually or when swallowed,
but the increase in exercise tolerance was
somewhat greater following sublingual admin-
istration. This drug was only of moderate
value in the treatment of patients with angina
pectoris.

Sodium nitrite was more effective when
given subcutaneously than when given sub-
lingually or when swallowed, but the degree
of value was low and the frequency of un-
toward reactions was too high to indicate
clinical value.

**SUMMARIO in INTERLINGUA**

Le valor comparative de 6 differente nitritos
in le tractamento de angina de pectore, admin-
istrate per via oral, sublingual, subcutaneae, e
percutaneae, esseva studiate in 34 patientes
per mesurar le quantitate de labor que poteva
esser executate sub conditiones standardisate
sin induction de angina e etiam per observar
le responsas clinie e le electrocardiogrammas
a exercitio.

Glycerol trinitrate, erythrol tetranitrate,
mannitol hexanitrate, e triethanolamino trini-
trate biphosphate esseva omnes plus efficace in
administration sublingual que post inglutition.
Nitroglycerina e erythrol tetranitrato, quando
administrate per via sublingual, es inter le
plus efficace de omne le agentes prophylactic
disponible pro le tractamento de patientes
con angina de pectore. Le comparativemente
prolongate duration del action de erythrol
tetranitrate post administration sublingual
rende iste agente specialmente utile pro usos
clinie.

Nitroglycerina e erythrol tetranitrate esseva
etiam efficace quando administrate per via
NITRITES IN THE TREATMENT OF ANGINA PECTORIS

parenteral or per inunction, sed lor valor esseva mucho restringite post inglutition. Iste observation suggere que le duo nitritos es inactivate in le vías gastrointestinal. Etiam manitol hexanitrate esseva plus efficace post uso sublingual que post inglutition, sed iste agente esseva de limitate valor clinico a causa del grande dimensiones del tabletas in que illo esseva disponibile. Triethanolamino trinitrate esseva moderamente efficace quando administrate sublingualmente e sin valor demonstrabile quando inglutite. Le uso terapeutic de iste droga es restringite a causa del frequentia de glossitis que seque su administration sublingual.

Pentaerythritol tetranitrate differeva paoco in le frequentia del responsa post administration sublingual e post inglutition, sed le augmento del toleration de exercitio esseva levemente plus marcate post administrationes sublingual. Iste droga esseva solmente moderamente utile in le tractamento de pacientes con angina de pector.

Nitrito de natrium esseva plus efficace quando administrate subcutaneamente que quando administrate sublingualmente o per inglutition, sed le grado de su valor esseva basse, e le incidentia de reactiones adverse esseva troppo frequente pro indicar un valor clinice.

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Nitroglycerin and Other Nitrites in the Treatment of Angina Pectoris: Comparison of Six Preparations and Four Routes of Administration
JOSEPH E. F. RISEMAN, GEORGE E. ALTMAN and SIDNEY KORETSKY

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