Amine Oxidase Inhibitors
Their Current Place in the Therapy of Cardiovascular Diseases

By George C. Griffith, M.D.

We have had a keen interest in the monoamine oxidase inhibitors (MAO-inhibitors) from the time that Cesaran reported their benefits in the prophylaxis of angina pectoris. Together with two of my associates, Dr. Robert W. Oblath and Dr. Willard J. Zinn, I have used four of the available MAO-inhibitors—iproniazid, isocarboxazid, beta-phenylisopropylhydrazine, and pivalylbenzhydrazine—in the treatment of patients with myocardial ischemia. In general we find that our patients feel better under medication with iproniazid and its analogues than they had felt prior to the administration of these products. They are more alert, more cheerful, and they can do more than was possible formerly. As other investigators have noted, under treatment with MAO-inhibitors patients previously disabled by angina are able to walk distances heretofore out of the question for them and—as long as they are receiving adequate dosages of these drugs—they can go about their daily activities within the limits dictated by the state of the myocardium and prescribed for them by their physicians without experiencing anginal pain or even pressure. Once the drug is stopped or reduced below the effective level for the individual patient, his capacity for effort again becomes increasingly limited, and he is forced to return to his pretreatment inactivity.

Patient-physician rapport is tremendously improved under the influence of the MAO-inhibitors. The patient assumes a healthier attitude toward his disease and a more hopeful outlook toward the future outcome. Whereas he remains aware of petty annoyances, he now reacts toward these with emotional detachment. Usually, tension and depression give way to a state of relative tranquility.

First employed for its tuberculostatic and tuberculoceidal properties alone, iproniazid administration was found to confer many other important benefits, of which at least two—relief of pain and the healing of mesodermal tissue—bear directly on the problem of pain prophylaxis in cardiovascular disease. Under iproniazid therapy the influence toward healing of mesodermal tissue has proved out of proportion to any influence of the chemical on the tubercle organism alone. Relief from pain has been such that in one patient with an extensive destructive neoplastic of the right pelvis, iproniazid administration has permitted increased hip movement and the discontinuance of 200 mg. of Demerol every 3 hours.2

Because of its potent appetite-stimulating effects, iproniazid has been employed with profit in the treatment of poor appetite due to hepatitis, cirrhosis, anorexia nervosa, poor nutritional state due to duodenal ulcer, ulcerative colitis, geriatric wasting, and chronic or psychogenic nausea without definite evidence of organic disease.3

As contentment and even feelings of elation often replace initial depression in tubercular patients maintained on iproniazid, this preparation and several of its analogues have been widely used in the treatment of hypoactive and depressed psychiatric patients. As anticipated, the antidepressive types of MAO-inhibitor are effective in most cases of depression, whatever the origin, and offer many advantages over electroconvulsive therapy, heretofore the only effective treatment of the depressed psychiatric patient.4 In addition to

From the Department of Medicine (Cardiology), University of Southern California School of Medicine, Los Angeles, Calif.
its beneficial effects on mood and activity, iproniazid administration has been found to increase physician-patient rapport: the patient both seeks and is additionally receptive to support and reassurance.

All these elements—pain relief, healing of mesodermal tissues, appetite stimulation, closer physician-patient rapport, and elevation of mood—are most important in the therapy of the patient with angina pectoris, who not only is limited in his capacity for effort but usually is very fearful of the outcome of his illness.

Biochemical and Physiologic Results of MAO-Inhibition

The effect of MAO-inhibitors on serotonin metabolism has received particularly close attention, inasmuch as iproniazid administration increases brain serotonin levels to 2 or 3 times normal. Following a single dose of iproniazid, the highest brain serotonin level is attained within 3 to 5 hours and tapers off within a few hours; repeated doses administered over several days do not raise brain serotonin levels above the concentration produced by a single dose. Iproniazid has been shown to have little effect on the peripheral metabolism of serotonin, with no increase of serotonin determinable in blood, stomach, or intestines, despite the marked increase in brain serotonin.

Apparently, iproniazid does not exert a significant effect on the concentrations of epi- nephrine or norepinephrine, the primary effect of iproniazid seems to be not on the level of the amines themselves but on their metabolites. As measured by the metabolism of methyl-labeled epinephrine, the biochemical effects of iproniazid in man persist for 2 or 3 weeks after cessation of iproniazid therapy. Some investigators believe that iproniazid may in some way convert the tension created by epinephrine into the euphoria often noted in the patient maintained on iproniazid—perhaps by the diversion of epinephrine or methoxepinephrine to adrenochrome or its derivatives. Patients who suffer from anxiety or tension destroy adrenochrome more rapidly than normal subjects do, and following the administration of adrenochrome or adrenolutin, anxiety steadily decreases.

The central stimulant effects of iproniazid appear to be due at least in part to the action of dopamine. Other amines that are affected by iproniazid administration include tyramine and tryptamine. In man, assay of urinary tryptamine affords a simple measure of MAO-inhibition that appears to be a reflection of MAO-inhibition throughout the body. Neurophysiologic studies suggest that central nervous stimulation of iproniazid probably is achieved through an effect on the hypothalamus. Possible Bases for Antianginal Effectiveness of MAO-Inhibitors

Since the admittedly fortuitous discovery by Cesaran that iproniazid relieves the pain of angina pectoris, a growing number of investigations have been designed to determine the possible bases for the alleviation of chest pain by these preparations. The first possible basis that comes to mind is, of course, a psychic element. Inasmuch as MAO-inhibitors purportedly increase physician-patient rapport and would therefore make the patient especially susceptible to the placebo effect so important in the evaluation of antianginal medications, careful double-blind investigations of the efficacy of MAO-inhibitors are most important, such as the study conducted by Shoshkes and his co-workers at Newark Beth Israel Hospital. In this 6-month study, 64 per cent of patients in this series received good or excellent relief from their angina within the first month on iproniazid (23 per cent, good; 41 per cent, excellent), and 72 per cent received good or excellent relief within the second month (10 per cent, good; 62 per cent, excellent). Substitution of the placebo caused a marked and sudden falling off of improvement, with only 5 per cent of the patients claiming excellent response and 25 per cent a good response. This would indicate that although a psychic element undoubtedly is involved in the effectiveness of iproniazid—as with any medication—this psychic element is not the most important or even a
major factor in the antianginal effect of the medication.

Hard to distinguish from the psychic element of angina and antianginal prophylaxis is the possibility of a specific rise in the pain threshold. For a time the belief was prevalent that the entire antianginal effect of these preparations is due to their antidepressant effect; however, the development of a number of MAO-inhibitors that further depress rather than increase drive and activity indicates that the noteworthy antianginal effect of the MAO-inhibitors is quite separate from their antidepressant effect. In table 1, 3 preparations that decrease rather than increase drive and activity are identified by asterisks.

Iproniazid, beta-phenylisopropylhydrazine, and related compounds have been shown to possess analgesic activity up to the efficacy of codeine. This analgesic activity is particularly noteworthy when mesenchymal tissues are involved, although MAO-inhibitors also have been used successfully to replace nar-
serotonin levels following MAO-inhibitors is important in the relief of angina pectoris: coronary dilatation is of very short duration, unlikely to provide chronic relief of anginal pain, and, as patients who need and respond to MAO-inhibitors usually suffer from advanced atherosclerosis of the coronary arteries, some question exists whether this type of diseased coronary artery would be able to dilate significantly in response to amine potentiation.

**Cardiovascular Effects of the MAO-Inhibitors**

In assessing the cardiovascular effects of the MAO-inhibitors, one must keep 3 factors in mind: the natural history of the disease, the recognized tendency for these patients to look for and to exaggerate the magnitude and importance of untoward reactions, and the placebo effect of the medications. At times it is difficult to ascertain whether events occurring during the course of medication have been caused by the medication or are the natural result of the underlying cardiovascular pathology.

**Effects on Blood Pressure**

Although instances of orthostatic hypotension stemming from the administration of iproniazid have been noted during the treatment of patients with tuberculosis and psychiatric depression, attention usually has been directed at the dangers of physical injury from falls attributable to hypotension, especially in elderly persons. Only recently has attention been focused on possible cardiovascular effects of the MAO-inhibitors. Investigators have been sharply divided into 2 camps: those who feel that the drugs should be withheld from persons with known cardiovascular impairment inasmuch as they tend to cause hypotension and thus may precipitate cerebrovascular accidents, and physicians who believe as strongly that such events are the natural occurrence in cerebrovascular disease and that the MAO-inhibitors do not increase the likelihood of cerebrovascular accidents. In general, we agree with the second group and, when indicated, we do not deny MAO-inhibitors to patients despite the presence of cerebrovascular disease.

The hypotensive effects of the MAO-inhibitors have led to their trial as antihypertensive agents, both alone and in combination with chlorothiazide, which has an antihypertensive tendency itself. Thus, Harnes noted a definite orthostatic hypotensive effect in 15 of 17 patients (88 per cent); in 5 of these patients, blood pressure was also reduced when in the supine position. Nussbaum reported the reduction of blood pressure in 17 of 22 hypertensive patients (77 per cent): 1 patient had been taken off mecamylamine, 15 mg. t.i.d.; when iproniazid, 50 mg. t.i.d., was substituted for the ganglion-blocking agent, his base blood pressure dropped from 170/140 without medication and 150/100 while he was receiving mecamylamine, to 110/70 while receiving iproniazid. Orvis and Tamagna and Maxwell have found iproniazid plus chlorothiazide or beta-phenylisopropylhydrazine plus chlorothiazide to constitute an effective antihypertensive regimen.

Patients with hypertension of severe degree require much decreased dosage of other antihypertensive medication to maintain safe blood pressure levels while taking MAO-inhibitors. Goldman discusses 1 patient who had required 800 mg. of hydralazine daily to maintain a level of 150 mm. systolic: this level was maintained with 150 mg. of iproniazid and only 100 mg. of hydralazine per day.

The action of beta-phenylisopropylhydrazine on blood pressure is similar to that of ganglion-blocking agents, according to Sjoerdsma et al. the MAO-inhibitor is superior in that it permits continual control with a once-a-day dose and avoids the side effects of impotency, mydriasis, and severe constipation. Cesarman, who considers iproniazid to be a ganglioplegic agent, reports that iproniazid is helpful in reducing blood pressure in patients who have not responded to or who have been unable to tolerate other blocking agents.

Cautioning that alterations in coronary circulation and consequent thrombosis may be induced by falls in blood pressure during shock, Master and Donoso suggest that MAO-inhibitors may be contraindicated in patients with regularly low blood pressure (less
than 100 mm. Hg, systolic), as often is the case in patients who have recently recovered from a coronary occlusion.

In an occasional patient, hypertension rather than hypotension results from the administration of MAO-inhibitors. One patient in our series, who had been maintained satisfactorily on iproniazid, developed hypertension when isocarboxazid was substituted for the iproniazid. Return of the patient to iproniazid resulted in a drop in blood pressure level toward but not to former levels.

Effect in the Anginal Syndrome due to Coronary Artery Disease

The MAO-inhibitors diminish both the intensity and frequency of anginal pain and increase the capacity for exertion. As Cesarman\(^\text{30}\) has noted, the greater the severity of pain, the more pronounced is the therapeutic response: After 90 days of treatment, 98 per cent of his patients who had had pain in clinostaticism were improved, as were 95 per cent who had had pain on slight exertion, 96 per cent who had had pain on moderate exertion, and 86 per cent who had suffered pain only with great exertion. Rivier\(^\text{39}\) has reported success in 75 per cent of 75 cases observed for periods of 2 to 11 months; Cossio\(^\text{39}\) has had good results in roughly 2 of 3 patients in a series of 300 whom he has maintained on the drug. These findings are typical of results in other series reported in the literature. We have found good or excellent results in about 70 per cent of our own patients.

There is some question whether the MAO-inhibitors merely exert a symptomatic effect or whether they possibly cause an increase in the efficiency of the heart muscle itself. Cesarman\(^\text{30}\) and Rivier\(^\text{38}\) believed that iproniazid must exert a direct action at the level of the myocardium. Master,\(^\text{40}\) Schweizer,\(^\text{41}\) and Wolfe and Shubin\(^\text{42}\) found no evidence that the underlying pathology is improved. If the MAO-inhibitors should result in significant improvement in the electrocardiogram, this might be interpreted as evidence that these preparations do improve myocardial action. Cesarman\(^\text{30}\) found favorable electrocardiographic modifications in some instances, which he suggests may be caused by a decrease in vasoconstrictor tone of the coronary vessels with increased coronary flow and cardiac output. Schweizer and von Planta,\(^\text{28}\) Cossio,\(^\text{39}\) and Master\(^\text{40}\) failed to note any improvement. Nevertheless, LaDue (personal communication) is reported to have noted improvement in the electrocardiograms of patients studied with his "walking electrocardiogram."

Effects on the Peripheral Vasculature

Reports of the effects of MAO-inhibitor administration on intermittent claudication are mixed, with several investigators\(^\text{42, 43}\) reporting intermittent claudication as occurring for the first time under MAO-inhibitor therapy, and others\(^\text{44}\) reporting dramatic benefit in this condition. Casselas\(^\text{46}\) described a patient who had been unable to walk 50 meters prior to iproniazid therapy, but who is able to walk a distance of 1,250 meters (1/4 mile) without pain or discomfort while on MAO-inhibitor therapy. Cossio\(^\text{45}\) found that half of the patients in his series could cover longer distances, yet in the end pain always forced them to stop and rest. Presumably, cases of intermittent claudication noted for the first time while the patient is under MAO-inhibitor therapy are not a direct effect of the drug: alleviation of anginal symptoms in these previously restricted persons enables them to walk, thereby making evident their latent peripheral circulatory insufficiency.\(^\text{42}\)

Color, temperature, and arterial oscillations remain unchanged in the distal segment of the lower limbs.\(^\text{45}\) Nevertheless, one instance of impending gangrene observed by Cossio\(^\text{45}\) showed an improved blood supply, which ruled out a probable amputation. Cossio found iproniazid very effective against the excruciating pain of impending gangrene. Sherbel and Harrison\(^\text{46}\) found an ointment containing 3 to 5 per cent of iproniazid ineffective when applied to ischemic ulcers associated with arteriosclerosis obliterans.

Infarction during MAO-Inhibitor Therapy

As serotonin is highly concentrated in the platelets, serotonin is believed to reduce the duration of local bleeding. Holtz\(^\text{47}\) has sug-
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gested that, as potentiatiors of serotonin, the MAO-inhibitors may influence the formation of thrombi and infarction. No evidence has been produced that this is indeed the case. There is evidence, however, that iproniazid administration may increase chances of survival if coronary occlusion occurs. As Regelson et al. have shown, iproniazid administered for 4 days prior to the onset of acute coronary occlusion prevents death in dogs by protecting them from the rapid onset of ventricular fibrillation.

Preparations Available for Use

As more and more MAO-inhibitors become available for clinical trial and, subsequently, for use in the treatment of cardiovascular problems and in other conditions, physicians will be able not only to tailor dosage to the individual needs of the patient but also to choose the specific MAO-inhibitor (or type of inhibitor) that will cause optimal improvement in the patient’s condition. Five preparations have undergone extensive clinical trials in this country: iproniazid, isocarboxazid, beta-phenylisopropylhydrazine, nialamide, and phenelzine.

Iproniazid

The first and most widely used of the MAO-inhibitors, iproniazid, is accepted as the standard of MAO-inhibitor action, and other preparations are referred to as having “so many times the potency of” iproniazid. When used in the massive dosages needed in the therapy of tuberculosis or even in the somewhat lesser dosages that first were used in the therapy of psychiatric patients, toxic side effects were common. One of the most serious of these side effects has been orthostatic hypotension, which necessitated interruption or discontinuance of therapy in a number of cases. As the newer analogues have been developed, they have to a considerable extent replaced iproniazid as the agent of choice. Some investigators still prefer to use iproniazid, either specifically for its hypotensive effect, or in small amounts (10 to 50 mg. daily) which apparently are useful in antianginal prophylaxis.

Even small doses such as 10 mg. of iproniazid per day can relieve severity and frequency of anginal seizures and increase exercise tolerance up to 50 per cent within 1 to 2 weeks, according to Grauman, who employed this small dosage successfully in treating 13 patients with severe to nearly intractable angina. All patients in this small series experienced mood elevation while on iproniazid; most striking antianginal benefits were achieved in those individuals in whom anxiety or a depressed state was an important feature. Master and Donoso, too, found that many patients could be maintained on small doses.

Isocarboxazid

This preparation purportedly is 7 times as effective as iproniazid in inhibiting MAO in vitro and 8 times as potent in potentiating the central nervous system action of 5-hydroxytryptophane in mice. Its action is far more potent in the brain (33 times that of iproniazid) than in the heart (8 times that of iproniazid). This increase in potency makes possible an average clinical dose of one quarter to one fifth that of iproniazid, and may be a factor in the reduction of frequency and severity of side effects reported with the newer preparation. We have employed 2 methods in administering isocarboxazid: in our younger and less seriously ill patients, we have started with the maximum dosage in order to reach full effectiveness within the shortest possible period; and we later have reduced dosage to the smallest amount that served to maintain the antianginal effect. In older and more seriously ill patients, we have administered smaller amounts and in divided doses. Although this might delay the energizing and antianginal effects of the drug, a wider margin of safety exists.

Over 70 per cent of our patients report appreciable benefit from isocarboxazid. We rarely have administered above 30 mg. per day: the majority of our patients have achieved maximum benefit with 15 to 30 mg. per day. This preparation has proved as effective as and frequently more effective than iproniazid, and sometimes is faster in onset of action.

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**Beta-phenylisopropylhydrazine**

Eight times as potent in inhibiting MAO in vitro as iproniazid, beta-phenylisopropylhydrazine is 40 times as effective in vivo in inhibiting heart MAO and 48 times as effective as iproniazid in inhibiting brain MAO.\(^\text{50}\) We have found isocarboxazid and beta-phenylisopropylhydrazine about equally effective in the prophylaxis of angina pectoris. Our customary procedure is to provide patients initially with 9 mg. of the preparation daily, in divided doses. In patients who receive complete relief of pain with this dosage, it later is reduced to 3 mg. twice daily. A reversible red-green color defect has been reported in a few patients on extended therapy with large doses of this agent.

Beta-phenylisopropylhydrazine has been used alone and in combination with chlorothiazide as an antihypertensive agent. As the MAO-inhibitors potentiate other hypotensive agents, lower doses of each are recommended.

**Nialamide**

This preparation is neither a stimulant nor a euphoriant. Nialamide has a relatively weak effect on brain MAO (about half the potency of iproniazid) and, perhaps for this reason, orthostatic hypotension has not been reported in clinical trials with this agent. As a rule, onset and development of the symptomatic effects are gradual. Wolfe and Shubin\(^\text{42}\) report over 50 per cent improvement in 46 of 59 patients who received nialamide for the relief of angina pectoris, although 26 of these patients had had intractable angina or status anginosus prior to institution of the drug. Administered to patients with myxedema following \(^{131}\) iodine therapy, nialamide permits the use of sufficient thyroid to relieve hypothyroid symptoms to a considerable extent without reinducing severe angina; nevertheless, it has not been possible to administer sufficient thyroid to eliminate the myxedema completely without producing recurrence of the anginal attacks.\(^\text{42}\)

Recommended initial dosage is 75 mg. of nialamide daily, in single or divided doses. After the first week, the daily dosage is revised upward or downward in steps of 12.5 or 25 mg., depending on the patient's tolerance. Once satisfactory response is obtained, dosage is reduced to the maintenance level.

**Phenelzine (Beta-phenylethylhydrazine)**

This potent, fast-acting MAO-inhibitor is reported to give good results in 80 to 85 per cent of patients with tension-fatigue states.\(^\text{51}\) Kimbal et al.\(^\text{52}\) reported that phenelzine markedly reduces the frequency and severity of migraine, and several investigators have found the drug to be of value in decreasing the number of attacks of angina pectoris. When given intravenously or intraduodenally to anesthetized dogs, phenelzine allegedly causes a marked increase in coronary blood flow with only minimal elevation of femoral arterial pressure. Dickel et al.\(^\text{51}\) found that even in cases in which phenelzine had no antidepressant effect, the drug nonetheless substantially improved the patient's ability to profit by psychotherapy.

Side effects have been relatively minor, with no positive laboratory report nor clinical evidence of organ damage or blood dyscrasias in 580 patients.\(^\text{53}\) Observed in only a few instances, orthostatic hypotension is most likely to occur in patients with low systolic pressures prior to therapy or in response to unusually large doses of the drug. The hypotension is not an indication for stopping therapy as it usually disappears within a few days or after reduction of dosage.\(^\text{53}\)

The recommended starting dosage for most patients is 45 mg. daily, in 3 divided doses. If no response occurs within a week, an additional 15 to 30 mg. may be given at bedtime. After a maximal clinical effect is secured (1 to 3 weeks) the dosage is gradually reduced to a maintenance dosage of about 15 mg. daily or every other day.\(^\text{53}\)

**Side Effects**

Reports of side effects during MAO-inhibitor therapy are frequent, but we must remember that in studies employing the double-blind technique, patients receiving placebo rather than MAO-inhibitor therapy also complain of headaches, dizziness, itching, nausea, weakness, tremors, diarrhea, and other untoward effects.
The only significant side effect we have encountered among our patients has been the occurrence of severe orthostatic hypotension in several patients who were maintained on iproniazid. Where needed for immediate effect, methoxamine was administered. Under less severe circumstances cortisone or hydrocortisone (12.5 mg. 1 to 3 times daily) or ACTH in a slowly absorbed form has yielded good results. Slight hypotension may be controlled by the concomitant administration of amphetamine or amphetamine-like preparations. Orthostatic hypotension has not been noted in the patients we have treated with pivalylbenzhydrazine.

Agitation has not been a serious problem among our patients. If noted, agitation can be controlled by the concurrent administration of phenelthiazine, or a nonstimulating type of MAO-inhibitor may be substituted for the MAO-inhibitor in use (table 1).

Periorbital or dependent edema may occur but usually will subside even without diuretic therapy after the second or third week. For faster response, dosage can be reduced slightly or a diuretic may be employed. As chlorothiazide is potentiated by the MAO-inhibitors, we prefer to use organomercurials for this purpose except in the instances in which we seek the potentiation of chlorothiazide’s antihypertensive effect.

Bladder or bowel dysfunction may be controlled by the administration of cholinergic stimulants, such as ambenonium or neostigmine. Hyperreflexia and hyperkinesis or muscle fasciculations are indications of excessive MAO-inhibitor dosage.

The administration of vitamin B₆ will prevent or correct instances of peripheral neuritis. We have not seen this side effect in our patients.

Both increases and decreases in sexual potency and activity have been noted under MAO-inhibitor therapy. Unless marked hypotension is present, alterations in sexual desires and activity usually disappear after a time without specific treatment.

Dietary precautions may be necessary to prevent unwelcome gain in weight. In some instances, the weight gain may be due to obstipation.

In the elderly patient especially, a sharp drop in systolic and diastolic blood pressure may result in decreased cardiac output with congestive failure and peripheral edema. Effects in these patients can be minimized by lowering the daily dose and administering the MAO-inhibitor in divided doses. Although this may delay energizing effects from 2 to 3 additional weeks, a wider margin of safety is provided by this practice.

Severe hepatitis has been reported to occur in patients undergoing iproniazid therapy, and a few instances of hepatitis have occurred in patients treated with the newer MAO-inhibitors. Although hepatitis probably will be extremely rare with the dosages now recommended, physicians must remember that these are potentially hepatotoxic materials and extreme caution must be exercised if they are employed together with other agents known or suspected to be hepatotoxic. We have had no instance of hepatitis or jaundice among our patients and attribute this in large measure to our continued alertness for signs or symptoms of impending toxicity or side effects of any sort.

Serial studies of hepatic function have occasionally yielded values outside the normal range, but no more frequently than similar values have appeared in tests of hepatic function in patients who are not on MAO-inhibitors. The abnormal values have without exception returned to within normal range during continued MAO-inhibitor therapy.

**Conclusion**

Development of the MAO-inhibitors unquestionably is an important forward step in the treatment of patients with angina pectoris. They also are useful in the treatment of hypertension. Provided patients are carefully observed for signs of any untoward effects and such tendencies are corrected immediately, side effects are exceedingly rare.

**Summario in Interlingua**

Le disvoloppamento de inhibitores de monoamino-oxydase es sin dubita un importante progresso in le
tratamiento de pacientes con angina de pecho. Tal inhibidores es etiam utile in lo tratamiento de hypertension. Providite que le pacientes es meticuloemente observable pro signos de efectos adverse e providite que tal tendentarios es corrigite immediateemente, efectos lateral es extremamente rar.

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