Effect of Alterations in Systemic Pressure upon Oxygen Saturation in Patients with Congenital Heart Disease

By RICHARD P. LASSER, M.D., AND GABRIEL GENKINS, M.D.

The effect of alteration of systemic pressure upon peripheral arterial oxygen saturation was studied in patients with congenital heart disease. Vasodepression produced by amyl nitrite caused a fall in systemic oxygen saturation in five patients with tetralogy of Fallot, two with patent ductus arteriosus and severe pulmonary hypertension, and one with Eisenmenger's complex. These changes did not occur in normals or in those with isolated pulmonic stenosis, trilection of Fallot, or uncomplicated interatrial septal defect or patent ductus. Levarterenol on the other hand produced a rise in systemic oxygen content in one patient with tetralogy of Fallot. The use of these technics is suggested as a diagnostic aid and for the study of venoarterial shunts.

PROMPTED by the observation of Hamilton et al.,1 in a patient with tetralogy of Fallot, that both a spontaneous decrease in systemic pressure and the administration of tetra-ethyl ammonium chloride were accompanied by a marked fall in systemic oxygen saturation, an effort was made deliberately to reproduce this sequence in a controlled fashion, by the use of drugs known to influence the systemic arteriolar resistance. The objective of this study was primarily to determine whether the response of the arterial saturation to changes in systemic pressure could be used in a diagnostic fashion in congenital heart disease, particularly to ascertain the presence of a communication between the aorta and right ventricle or pulmonary artery. Such information would help reveal potential veno-arterial shunts in acyanotic subjects with tetralogy of Fallot, Eisenmenger’s syndrome or patent ductus arteriosus with pulmonary hypertension.

Amyl nitrite was selected as a vasodepressor agent because it had been shown to relax the tone of systemic arterioles and muscular arteries without affecting similar vessels of the pulmonic circuit.2 This drug also possesses other desirable properties: (1) Its effect is quite transient, thus avoiding prolonged depression of systemic pressure, (2) the effect is immediate, (3) the cooperation of the patient is not required, and the drug can be administered to anesthetized subjects.

The second drug tested was levarterenol (Levophed). This pressor agent is known to increase the tone of the systemic arteries and arterioles but has only a weak action, if any, upon the pulmonary vasculature. It was felt that a pressor drug might produce a rise in peripheral oxygen saturation in the same cases of congenital heart disease in which vasodepressor effects are accompanied by a fall in saturation.

Both drugs have secondary circulatory effects, so that their actions cannot be considered solely as peripheral ones. Amyl nitrite causes increased venous return and an arterial pressure overshoot in the recovery phase.2 Levarterenol has a primary cardiac inotropic action,3, 4 and has been shown to produce mild pulmonary vasoconstriction in dogs.5

MATERIAL AND METHODS

Studies of the effect of amyl nitrite were carried out without adverse reaction during the course of 32 routine diagnostic cardiac catheterizations. Eleven of these studies are excluded as unsatisfactory for the following reasons: Satisfactory arterial samples were not obtained in four; in two patients a prolonged period of time elapsed between the control and test samples; in one infant no fall in arterial pressure was recorded and it was assumed that insufficient amyl nitrite had been inhaled; four studies were omitted because of uncertain diagnosis. The 21 satisfactory studies reported include normal subjects and tetralogy of Fallot, isolated pulmonic stenosis, uncomplicated interatrial septal defect, atrioventricular canal...
SYSTEMIC PRESSURE AND OXYGEN SATURATION

(ostium primum type), patent ductus arteriosus, interventricular septal defect and Eisenmenger's complex. One patient with mitral stenosis was also included.

Levarterenol was administered to one subject with isolated pulmonic stenosis and one with tetralogy of Fallot.

Cardiac catheterization was performed in the usual fashion in all patients. Adults were premedicated with oral secobarbital (Sodium Seconal), 90 mg. Children received either tribromoethanol (Avertin) 90 mg./Kg. rectally or morphine sulfate, 0.2 mg./Kg. subcutaneously. In the younger patient supplemental anesthesia, when necessary, was administered through the catheter as a 0.02 per cent solution of thiopental sodium (Sodium Pentothal).

A Cournand or Reilly indwelling arterial needle was inserted into a femoral or brachial artery to permit recording of arterial pressure and collection of blood samples. Oxygen analysis was performed in the standard Van Slyke-Neill manometric method, with duplicate checks on each sample. Oxygen content of these duplicates were required to check within 0.2 volumes per cent. Pressure records were obtained through Statham P23A and 23AA transducers attached to a multichannel oscillographic recorder.*

Simultaneous records at equal sensitivity were obtained wherever possible of right ventricular and peripheral arterial pressure, and the latter pressure was observed upon a monitor screen during the entire test procedure. After suitable control recording, an amyl nitrite "pearl" (0.2 ml. of 90 per cent amyl nitrite) was crushed, wrapped in a thin towel, placed over the patient's nose and mouth and held there for two breaths. The time of first inhalation was recorded. Experience revealed that the nadir of arterial pressure was usually reached within 20 to 30 sec. after the first inhalation. Therefore test sampling was routinely started at 30 sec. and was completed 20 sec. later. The time interval between the control and test arterial samples was never more than 5 min.

Levarterenol was prepared by mixing 2 ml. of the concentrated solution (2 mg.) in 500 ml. of a 5 per cent dextrose solution. This mixture was administered via the cardiac catheter into the right ventricle. Continuous observation made it possible to elevate arterial pressure to any desired level by controlling the rate of administration.

To test variability of oxygen content in successive arterial samples in the same patient under test conditions, a series of 30 consecutive cases of mitral stenosis was reviewed. In these patients arterial samples had been obtained during cardiac catheterization, at rest and at exercise. The maximal range of variation of oxygen content observed was ± 0.4 volumes per cent.

RESULTS

The results of the 21 satisfactory studies are shown in table 1. Group A includes those patients who experienced no change in oxygen content, i.e., four patients without heart disease, one with mitral stenosis, three with isolated pulmonic stenosis, one with trilogy of Fallot, two with interatrial septal defect without pulmonary hypertension, one with uncomplicated patent ductus arteriosus and one case of atroventricular canal with marked pulmonary hypertension. The maximum decrease in arterial oxygen content observed in these thirteen studies was 0.4 vol. per cent. This value is not significant since it is within the limit of variability for successive samples in individuals without possible venoarterial shunts as previously described. The average decrease of systolic arterial pressure in this group was 16.4 mm. Hg and the parallel diastolic change was 12.8 mm. The systolic change varied between 2.5 and 28.6 mm. Hg.

Group B patients manifested significant decreases in oxygen content. They included one case of Eisenmenger's complex, five cases of tetralogy of Fallot and two instances of patent ductus associated with pulmonary hypertension.

Patient B.R. (Eisenmenger's complex) experienced a fall in arterial oxygen content of 1.0 vol. per cent during the response to amyl nitrite. Systemic arterial pressure decreased by 28/24 mm. Hg. The decrease in oxygen content observed indicates that venoarterial shunting had occurred (fig. 1).

Patient D.S. (tetralogy of Fallot) demonstrated the most marked fall in arterial oxygen content, 8.4 volumes per cent (saturation changed from 78 to 21 per cent). This dramatic change was occasioned by a fall in systemic systolic pressure of about 15 mm. Hg as observed on the monitor screen. The effect was transient and return of arterial pressure to original levels occurred within 60 sec. Despite these extremely low oxygen values, no signs of cerebral anoxia were noted at this

*Electronics for Medicine.
Table 1.—Systemic Arterial Oxygen Data and Pressure Values with Amyl Nitrite

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Pre-test Oxygen Cont.</th>
<th>Pre-test Sat.</th>
<th>Test Oxygen Cont.</th>
<th>Test Sat.</th>
<th>Pressures (mm. Hg) Pre-test</th>
<th>Test</th>
<th>Diagnosis</th>
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<tbody>
<tr>
<td>MK</td>
<td>18</td>
<td>18.8</td>
<td>97</td>
<td>18.8</td>
<td>97</td>
<td>136/80</td>
<td>124/72</td>
<td>Normal</td>
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<tr>
<td>WF</td>
<td>10</td>
<td>15.9</td>
<td>93</td>
<td>15.9</td>
<td>93</td>
<td>94/57</td>
<td>91/55</td>
<td>Normal</td>
</tr>
<tr>
<td>MC</td>
<td>4</td>
<td>13.7</td>
<td>89</td>
<td>13.4</td>
<td>87</td>
<td>92/58</td>
<td>49/28</td>
<td>Normal</td>
</tr>
<tr>
<td>AT</td>
<td>10</td>
<td>16.2</td>
<td>96</td>
<td>16.1</td>
<td>95</td>
<td>Pressures not recorded</td>
<td></td>
<td>Normal</td>
</tr>
<tr>
<td>ED</td>
<td>57</td>
<td>16.8</td>
<td>91</td>
<td>16.5</td>
<td>89</td>
<td>131/67</td>
<td>126/65</td>
<td>Mitral stenosis</td>
</tr>
<tr>
<td>VE</td>
<td>50</td>
<td>19.6</td>
<td>95</td>
<td>19.8</td>
<td>96</td>
<td>135/88</td>
<td>116/83</td>
<td>P.S.</td>
</tr>
<tr>
<td>HA</td>
<td>11</td>
<td>18.4</td>
<td>93</td>
<td>18.5</td>
<td>95</td>
<td>Pressures not recorded</td>
<td></td>
<td>P.S.</td>
</tr>
<tr>
<td>ET</td>
<td>7</td>
<td>16.2</td>
<td>91</td>
<td>16.1</td>
<td>91</td>
<td>114/49</td>
<td>98/51</td>
<td>Trilogy of Fallot</td>
</tr>
<tr>
<td>AK</td>
<td>5</td>
<td>14.4</td>
<td>95</td>
<td>14.4</td>
<td>93</td>
<td>Pressures not recorded</td>
<td></td>
<td>P.S.</td>
</tr>
<tr>
<td>EA</td>
<td>19</td>
<td>17.3</td>
<td>97</td>
<td>16.9</td>
<td>94</td>
<td>Pressures not recorded</td>
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<td>IASD</td>
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<tr>
<td>SS</td>
<td>33</td>
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<td>98</td>
<td>20.2</td>
<td>98</td>
<td>105/46</td>
<td>98/38</td>
<td>PDA</td>
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<tr>
<td>BR</td>
<td>9</td>
<td>15.4</td>
<td>92</td>
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<td>80/52</td>
<td>60/40</td>
<td>IASD</td>
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<tr>
<td>STS</td>
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<td>14.4</td>
<td>89</td>
<td>14.1</td>
<td>87</td>
<td>98/56</td>
<td>70/42</td>
<td>AV canal</td>
</tr>
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</table>

Group B

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Pre-test Oxygen Cont.</th>
<th>Pre-test Sat.</th>
<th>Test Oxygen Cont.</th>
<th>Test Sat.</th>
<th>Pressures (mm. Hg) Pre-test</th>
<th>Test</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bito</td>
<td>14</td>
<td>18.8</td>
<td>92</td>
<td>17.8</td>
<td>87</td>
<td>121/64</td>
<td>93/40</td>
<td>Eisenmenger</td>
</tr>
<tr>
<td>DS</td>
<td>2</td>
<td>11.5</td>
<td>78</td>
<td>3.1</td>
<td>21</td>
<td>98/63</td>
<td>15 mm less</td>
<td>Tetralogy</td>
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<tr>
<td>BM</td>
<td>1</td>
<td>13.1</td>
<td>73</td>
<td>10.5</td>
<td>59</td>
<td>66/43</td>
<td>54/32</td>
<td>Tetralogy</td>
</tr>
<tr>
<td>GP</td>
<td>5</td>
<td>14.3</td>
<td>84</td>
<td>12.2</td>
<td>72</td>
<td>110/66</td>
<td>105/57</td>
<td>Tetralogy</td>
</tr>
<tr>
<td>AW</td>
<td>35</td>
<td>19.7</td>
<td>80</td>
<td>18.6</td>
<td>76</td>
<td>131/91</td>
<td>114/78</td>
<td>Tetralogy</td>
</tr>
<tr>
<td>KP</td>
<td>2</td>
<td>16.5</td>
<td>91</td>
<td>12.0</td>
<td>67</td>
<td>83/57</td>
<td>61/40</td>
<td>Tetralogy</td>
</tr>
<tr>
<td>AZ</td>
<td>3</td>
<td>14.4</td>
<td>89</td>
<td>15.6</td>
<td>84</td>
<td>122/46</td>
<td>116/47</td>
<td>PDA with PH</td>
</tr>
<tr>
<td>AD</td>
<td>5</td>
<td>14.5</td>
<td>88</td>
<td>13.3</td>
<td>81</td>
<td>67/36</td>
<td>56/32</td>
<td>PDA with PH</td>
</tr>
</tbody>
</table>

Cont. oxygen content in volumes per cent; Sat. per cent saturation; P.S., isolated pulmonic stenosis; IASD, interatrial septal defect; PDA, patent ductus arteriosus; AV canal, atrioventricular canal; IV, interventricular septal defect; PH, pulmonary hypertension.

time while the child was under anesthesia (intravenous pentothal). Immediate and subsequent neurologic examination failed to reveal any abnormality. This patient was a severely ill two-year-old child with marked arterial desaturation at rest and was subject to the frequent attacks of intense cyanosis and syncope which occur in severe cases of tetralogy of Fallot.

Patient B.M. (tetralogy of Fallot) was one in whom simultaneous pressure records were obtained in the right ventricle and brachial artery during the test procedure. Right ventricular pressure declined 1.9 mm. Hg while systemic arterial systolic pressure declined 12 mm. Hg. This differential effect accounts for the preferential shunting of venous blood into the aorta. In this case arterial oxygen decreased by 2.6 volume per cent.

The next two patients with tetralogy of Fallot, G.P. and A.W., experienced moderate falls of arterial oxygen content of 2.1 and 1.1 volumes per cent respectively. The final patient with tetralogy of Fallot, K.P., demonstrated a decrease of oxygen content of 4.5 volumes per cent, from 91 to 67 per cent. This two-year-old child, while not markedly cyanotic at rest, had nevertheless experienced...
several spontaneous attacks of deep cyanosis and syncope within the previous few months.

It is interesting to note that while all patients with tetralogy of Fallot studied responded to the test with a fall in oxygen saturation, the two who showed an exaggerated response, D.S. and K.P., were the only ones who had experienced repeated spontaneous attacks of deep cyanosis and syncope prior to the test. The response to amyl nitrite thus demonstrated that in these two cases marked desaturation accompanied only mild falls in pressure such as might occur during ordinary activities like postural change, quiet standing, or the performance of a Valsalva maneuver during crying, coughing or straining.

The two patients with patent ductus and pulmonary hypertension showed mild desaturation in the femoral artery control specimens before the test, indicating some reversal of flow through the ductus. In both cases the arterial oxygen content decreased further during the test procedure (0.8 and 1.2 volumes per cent) with only relatively minor falls in arterial pressure.

The responses of patients to levarterenol are presented in table 2. W.D. (isolated pulmonic stenosis) experienced marked increase in arterial (101/64 to 180/88) and right ventricular (100/8 to 160/16) pressures. No significant change in arterial oxygen content was noted. The administration of levarterenol to one of the patients with tetralogy of Fallot, A.W., resulted in a rise of arterial content of 1.7 per cent concomitant with a rise of systemic arterial pressure of 36 mm. Hg. A return of oxygen content to the control level was noted upon discontinuation of the infusion and return of pressure level to resting values. The later administration of amyl nitrite in this same patient was shown to decrease arterial oxygen content by 1.1 volume per cent.

**Discussion**

Amyl nitrite is somewhat irritating and its pungent odor may occasionally frighten the
TABLE 2.—Effect of Levarterenal Infusion Upon Arterial Oxygen Saturation and Blood Pressure

<table>
<thead>
<tr>
<th>Condition</th>
<th>Oxygen saturation (per cent)</th>
<th>Systemic pressure (mm Hg)</th>
<th>Rt. vent. pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Test</td>
<td>Control</td>
</tr>
<tr>
<td>Isolated pulmonic stenosis</td>
<td>93</td>
<td>84</td>
<td>101</td>
</tr>
<tr>
<td>Tetralogy of Fallot</td>
<td>79</td>
<td>83</td>
<td>127</td>
</tr>
</tbody>
</table>

younger patient. The induction of light anesthesia has eliminated breath holding, turning of the head and similar technical difficulties. Adults experience no difficulty with the test procedure, and in them such factors do not enter into the production of the “positive” response.

In evaluating and defining the limits of a positive response to amyl nitrite two main pertinent factors were considered. The first was the accuracy of the laboratory determination of oxygen content in consecutive samples in the same patient. In a survey of 30 consecutive cases of mitral stenosis studied in our laboratory under conditions of rest and standard exercise, the maximum difference between any two paired specimens did not exceed ± 0.4 volume per cent. The second is the comparison of arterial samples taken before and after inhalation of amyl nitrite in patients without possibility of venoarterial shunt. This was done in the four normal patients and in one patient with mitral stenosis. Again, the maximum observed difference in oxygen content of these paired specimens proved to be less than ± 0.4 volume per cent.

A difference within this range therefore can be considered as the maximal permissible variation of oxygen content to be expected in patients without vascular or intracardiac shunts in response to the inhalation of amyl nitrite. Despite this rather clear-cut range of variation, we considered a positive response to entail a change of at least 0.8 volume per cent, believing that variation between 0.4 and 0.8 volume per cent cannot be evaluated properly with the present experience.

Positive responses thus occurred in a group of patients with certain features in common. One was the factor of a communication between right ventricle and aorta or pulmonary artery and aorta, in combination with either pulmonic stenosis or a high pulmonary artery pressure or vascular resistance. Right ventricular hypertension is the common denominator. Although cases of significant venoarterial shunting through interatrial septal defects were not observed, our experience is still limited in this regard.

The mechanism of the positive response is believed to be that originally proposed by Hamilton. The cardiac lesions in which a positive test occurred were those in which the right ventricle functions as a “double outlet” pump. The proportion of right ventricular ejectate which flows into either orifice appears to depend upon the relative resistance of the two circuits. Pulmonary resistance is thus governed by either pulmonic stenosis (valvular or infundibular) or by the vascular resistance offered by spasm or structural narrowing of the smaller pulmonary arterial radicles. The resistance of the systemic circulation depends upon the accessibility of the aortic orifice (degree of functional or structural over-riding) and the peripheral vascular bed. Amyl nitrite decreases this latter factor primarily and right ventricular output is shunted preferentially into the aorta. The actual volume of shunted blood depends upon anatomic factors and the magnitude of peripheral pressure change. While these studies reveal that this pressure change need only be minimal to effect significant changes in oxygen saturation of susceptible cases, Hamilton demonstrated marked vasodepression in association with arterial desaturation. Wood reported five cases of tetralogy of Fallot observed during spontaneous syncope in whom no appreciable fall of systemic blood pressure was noted. He concluded, therefore, that such attacks are initiated by spasm of the infundibular region of the right ventricle producing increased resistance to ejection into the pulmonary artery. Both mechanisms seem potentially operative as both have been observed experimentally and spontaneously.

Consideration of the right ventricle in this fashion also tends to explain the action of...
levarterenol in raising peripheral arterial oxygen content. As the systemic vascular resistance is raised by this drug, there occurs a decrease in the volume of venoarterial shunting as the right ventricular output seeks what is now the path of lesser resistance into the pulmonary artery. The actions of levarterenol upon the intact circulation, however, are varied. As seen in the patient with pulmonic stenosis and in experimental animals,3, 4, 7 increase of the force of right ventricular contraction occurs with this drug. In the case presented there was also a rise in right ventricular diastolic pressure, indicating the limited degree of myocardial reserve present. Vasoconstrictor effects of levarterenol have been demonstrated in the small vessels of the lung.8 Such effects are probably of small significance, particularly in patients with tetralogy of Fallot, when compared with the marked rise in peripheral vascular resistance. In such a patient the use of pressor drugs to improve arterial oxygen saturation is therefore suggested.

In a reverse fashion pressure in the pulmonary circuit may be selectively decreased by various agents when pulmonary hypertension is present. Burchell et al.8 demonstrated this effect through the inhalation of 100 per cent oxygen in cases of patent ductus with partial venoarterial (reversed) shunt. As the pulmonary arterial pressure was depressed by the oxygen to a greater degree than peripheral pressure, the reversed shunt was abolished. Increase of reversal could be produced by inhalation of low oxygen mixtures, which further and selectively increased pulmonary artery pressure.

Diagnostic application of this type of study is suggested in cases where potentiation of the shunt is needed to make its presence evident. Such would be cases of "cyanotic tetralogy of Fallot" in which depression of peripheral resistance may intensify a venoarterial shunt that is minimal under conditions of rest. Differentiation from cases of isolated pulmonic stenosis may thus be possible without further elaborate procedures.

Summary

Studies have been made with a vasodilator drug, amyl nitrite, and a vasopressor agent, levarterenol, in patients with congenital heart disease. Five cases of tetralogy of Fallot, two with patent ductus arteriosus and severe pulmonary hypertension, and one with interventricular septal defect and marked pulmonary hypertension (functional Eisenmenger's complex), manifested a decrease in arterial oxygen content and saturation in response to a fall in systemic arterial pressure. In one patient with tetralogy of Fallot, a rise in arterial oxygen content was produced by the administration of levarterenol. These changes in oxygen content were not observed in normal subjects, or in subjects with isolated pulmonic stenosis or congenital cardiac lesions characterized by left to right shunt without pulmonary hypertension. The possibility of this relationship for diagnostic purposes is therefore suggested. Amyl nitrite is thought to be suitable because the reaction is very transient and moderate, with return of pressure to control levels within one minute. As it does not require cooperation by the patient, it can be administered to an anesthetized subject of any age. The observation that a pressor drug is capable of raising the systemic oxygen content in patients with tetralogy of Fallot suggests that a trial of drug-induced hypertension might be made.

Acknowledgment

We wish to thank Dr. Alvin J. Gordon, chief of the cardiac catheterization team of the Mount Sinai Hospital, and its other members, for their assistance in carrying out these studies.

Summario in Interlingua

In patientes con congenite morbo cardiac, studios esseva effectuate con un droga vasodilatori, nitrito de amyllo, e un droga vasopressori, levarterenol. Cinque patientes con tetralogia de Fallot, duo patientes con patente ducto arterioso e sever hypertension pulmonar, e un patiente con defecto de septo interventricular e marcate hypertension pulmonar (functional complexo de Eisenmenger) manifestava un reduction del contenu e del satura-
tion arterial de oxygeno in responsa a un reduction del tension arterial in le circulation systemic. In un paciente con tetralogia de Fallot, un augmento del contento arterial de oxygeno esseva producite per le administration de levarterenol. Iste alterationes in le contento de oxygeno non esseva observate in subjectos normal o in subjectos con isolate stenosis pulmonic o congenite lesiones cardiac characterisate per un shunt sinistro-dextere sin hypertension pulmonar. Se suggere per consequente le possibilitate que iste relationes es de valor pro objectivos diagnostic. Nitrito de amylo es considerate como utile a causa del facto que su reaction es transient e moderate, con le retorno del tension a nivellos de controlo intra un minuta. Viste que su application non require le cooperation del patiente, illo pote esser usate in subjectos anesthesiate de omne etates. Le observation que un agente vaso-pressori es capace a augmentar le contento systemic de oxygeno in patientes con tetralogia de Fallot suggere que in tal casos le induction medicamentos de hypertension merita esser essayate.

REFERENCES
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