# Comparative Cardio-Inhibitory Effects of Certain Cyclohexanol and Cyclohexylamine Derivatives

By D. C. KOSEGARTEN, J. J. DEFEO, and D. R. DEFANTI

**Derivatives of cyclohexanol and cyclohexylamine were screened for cardioplegic effects on intact anesthetized rats and isolated guinea pig hearts. Evaluation of potency was based on the ability of the compounds to depress rat carotid blood pressure, and to produce reversible arrest of the isolated guinea pig heart. *trans*-2-*o*-Tolyl-*cis*-1,4-cyclohexanediol and *trans*-2-*o*-tolyl-*trans*-1,5-cyclohexanediol were equally effective and the most active compounds tested in producing a hypotensive response. *trans*-2-(*p*-Chlorophenyl)-*N*,*N*-dimethylcyclohexylamine was the least active and the only compound causing a pressor response. As a group, the cyclohexanol derivatives were more potent hypotensive agents than were the derivatives of cyclohexylamine. Conversely, the cyclohexylamines were more potent cardioplegic agents. The *cis* and *trans* isomers of 2-(*p*-chlorophenyl)-*N*,*N*-dimethylcyclohexylamine were equally the most active, with *trans*-2-*o*-tolyl-*cis*-1,4-cyclohexanediol the least active of the compounds studied. The minimum effective cardioplegic dose of 1-ethynyl-*trans*-2-*o*-tolylcyclohexanol was also the cardiotoxic dose as the heart failed to recover from arrest. Mechanism studies indicate an antagonistic effect between calcium and the negative inotropic action of these compounds.**

TODAY "open-heart" surgery has changed the outlook for a great many cardiac patients, particularly those having congenital defects, who would have been labeled as hopeless cases slightly more than 10 years ago.

An important aid in the surgical treatment of intracardiac defects is the still heart. Under certain conditions, where a dry, motionless, and clearly visible operative field is desirable, an arrested and all but bloodless heart enables the surgeon to repair more accurately a particular defect.

Elective cardiac arrest has been experimentally and clinically produced by several methods; for a review see Stephenson (1). These consist chiefly of producing arrest by hypothermia, myocardial anoxia, pharmacological agent, or a combination of any or all three.

In 1959 Huitric *et al.* (2) reported that 2-(*o*-tolyl)-cyclohexanol was capable of producing reversible cardiac arrest, without affecting myocardial electrical properties. This finding stimulated the preparation of a number of cyclohexanol and cyclohexylamine derivatives by Huitric.

Previous pharmacologic studies by Smookler and DeFeo (3) and Smith (4) showed the degree of cardio-inhibitory activity to be related to the functional groups and stereochemistry of these compounds.

In continuation therefore, the present investigation was carried out on additional compounds prepared by Huitric, in an effort to determine their possible cardio-inhibitory activity and its relationship to molecular structure.

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## EXPERIMENTAL

**Materials**—The cyclohexylamine hydrochloride salts (Fig. 1) were freely soluble in water. The ethynyl derivatives of cyclohexanol (Fig. 2) were practically water insoluble, while the remaining cyclohexanol derivatives (Fig. 2) were slightly water soluble. Accordingly, the ethynyl derivatives were dissolved in 50% polyethylene glycol (PEG) 400, while aqueous solutions of the remaining cyclohexanol derivatives, as well as the cyclohexylamine hydrochloride salts were used throughout the investigation.

**Rat Blood Pressure**—Male albino rats (260 Gm., average weight) were anesthetized with an intraperitoneal injection of 1.2 Gm./Kg. of urethan. The effects were recorded on a slowly moving smoked kymograph by direct cannulation of the right carotid artery *via* a fluid bridge of normal saline connecting the cannula to a mercury manometer. Injections of the test compounds were made intravenously and not more than six injections were made during one experiment.

Dosage was adjusted according to the results obtained, in order to determine the dose of a particular compound that would produce a 50% drop in the blood pressure. Dose and response were subjected to linear regression computations and the dose producing a 50% drop in blood pressure ($ED_{50}$) calculated. The ethynyl derivatives of cyclohexanol could not be tested, as the solvent used for these compounds possessed an effect of its own on the blood pressure of the intact rat.

In an effort to account for the pressor response to TH-25 the experimental procedures were modified. The preparation was allowed to stabilize for 20 min. and then the following trials were carried out at 5-min. intervals: (*a*) occlusion of the left common carotid artery for 10 sec., (*b*) 0.06 ml. of epinephrine 1:100,000, (*c*) 4 mg./Kg. TH-25, (*d*) 20 mg./Kg. i.v. hexamethonium, (*e*) 10-min. pause to allow preparation to stabilize and then repeat tests (*a*),

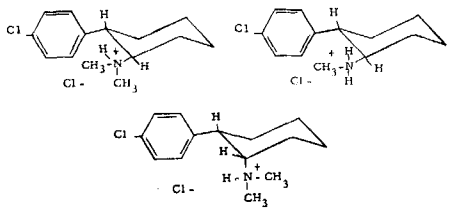

*Fig. 1—Cyclohexylamine hydrochloride derivatives. Top left:* trans-*2*-(p-*chlorophenyl*)-N,N-*dimethylcyclohexylamine hydrochloride* (*TH-25*). *Top right:* trans - *2* - (p - *chlorophenyl*) - N - *methylcyclohexylamine hydrochloride* (*TH-26*). *Bottom:* cis-*2*-(p-*chlorophenyl*)-N,N-*dimethylcyclohexylamine hydrochloride* (*TH-27*).

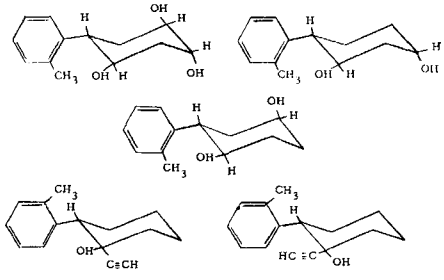

*Fig. 2—Cyclohexanol derivatives. Top left:* trans-*2*-o - *tolyl* - cis - *4* - *hydroxy* - trans - *5* - *hydroxycyclohexanol* (*CH-21*). *Top right:* trans-*2*-o-*tolyl*-trans-*1,5-cyclohexanediol* (*CH-20*). *Middle:* trans-2-o-*tolyl*-cis-*1,4-cyclohexanediol* (*CH-14*). *Bottom left: 1-ethynyl*-trans-*2*-o-*tolylcyclohexanol* (*AH-64*). *Bottom right: 1-ethynyl*-cis-*2*-o-*tolylcyclohexanol* (*AH-65*).

(*b*), and (*c*). The per cent change in blood pressure produced by TH-25 before and after the administration of hexamethonium was the index of activity studied.

**Isolated Guinea Pig Heart**—Guinea pigs of either sex were sacrificed by cervical dislocation. The heart was rapidly removed and was suspended after cannulation of the aorta in an Anderson-Craver perfusion apparatus. The perfusion solution used was that recommended by Chenoweth and Koelle (5), slightly modified by Smookler and DeFeo (3), and saturated with a continual flow of 95% oxygen and 5% carbon dioxide. The fluid level in the perfusion well of the apparatus was kept constant with the aid of a glass siphon tube placed in the upper end of the well. Excess fluid was thus collected with the aid of a pump and returned to the perfusion fluid reservoir. The preparation was maintained at 37.5° and the heart perfused under a head pressure of 54 cm. of water. Isotonic ventricular contractions were recorded on a slowly moving smoked kymograph. Only one compound was tested in each experiment of not more than five injections. A control dose of 50% PEG was injected at the beginning and end of each experiment involving the ethynyl derivatives of cyclohexanol.

A negative inotropic response of 95% or more was considered to be cardiac arrest and recovery was allowed to take place spontaneously. Dose and response were subjected to linear regression computations and the dose producing cardiac arrest ($ED_{95}$) calculated.

**Isolated Rat Atria**—Male albino rats were killed by cervical dislocation and hearts rapidly excised. The atria were freed of ventricular muscle and connective tissue, and suspended vertically in an 8-ml. tissue bath. The bathing solution (same as above) was continually aerated with a mixture of 95% oxygen and 5% carbon dioxide, and temperature maintained at 29° as suggested by Burn and Vane (6). Amplitude of isotonic contractions and the rate of spontaneous beat were recorded under a resting tension of approximately 0.75 Gm. on a smoked kymograph.

CH-20 and TH-27 were chosen to be tested in conjunction with a 4% calcium chloride solution, to study the mechanism involved in the cardioplegia produced by each series of compounds. At least 3 min. were allowed for the compounds to act on the suspended tissue. A minimum of three washes over a period of 5 min. were performed between trials, and the tissue allowed an additional 5-min. recovery period before proceeding to the next trial.

## RESULTS AND DISCUSSION

**Rat Blood Pressure**—CH-21 in doses of 1.0 to 12.0 mg./Kg. produced a drop in mean blood pressure ranging from 22 to 80% of the normal. CH-14 in doses of 2.0 to 8.0 mg./Kg. produced a drop in mean blood pressure of 35 to 85%. CH-20 in doses of 2.0 to 8.0 mg./Kg. produced a drop in mean blood pressure of 42 to 63%. TH-26 in doses of 2.0 to 18.0 mg./Kg. produced a drop in mean blood pressure of 5 to 42%. TH-27 in doses of 2.0 to 14.0 mg./Kg. produced a drop in mean blood pressure of 20 to 57%.

Duration of response was not linear with the cyclohexanol derivatives, and varied from 50 to 400 sec. Conversely, the duration of the hypotensive response to the cyclohexylamine derivatives was linear from 25 to 74 sec. with 2.0 to 6.0 mg./Kg. of TH-26, and from 25 to 130 sec. with 2.0 to 8.0 mg./Kg. of TH-27.

The hypotensive $ED_{50}$ of each of the above compounds is shown in Table I. Omitted from the table is TH-25, which in doses of 4.0 to 8.0 mg./Kg. produced a rise in mean blood pressure (Fig. 3) of 20 to 28%, with a linear duration in pressor response from 44 to 108 sec.

TABLE I—COMPARISON OF THE $ED_{50}$ (HYPOTENSIVE) OF THE NONETHYNYL CYCLOHEXANOL DERIVATIVES AND THE CYCLOHEXYLAMINE DERIVATIVES ON THE BLOOD PRESSURE OF RATS

| Compd. | Total Trials | Calcd. $ED_{50}$, mg./Kg. |
|---|---|---|
| *trans*-2-*o*-Tolyl-*cis*-4-hydroxy-*trans*-5-hydroxycyclohexanol (CH-21) | 18 | 5.30 |
| *trans*-2-*o*-Tolyl-*cis*-1,4-cyclohexanediol (CH-14) | 11 | 3.95 |
| *trans*-2-*o*-Tolyl-*trans*-1,5-cyclohexanediol (CH-20) | 12 | 4.04 |
| *trans*-2-(*p*-Chlorophenyl)-*N*-methylcyclohexylamine HCl (TH-26) | 20 | 26.30 |
| *cis*-2-(*p*-Chlorophenyl)-*N,N*-dimethylcyclohexylamine HCl (TH-27) | 16 | 12.94 |

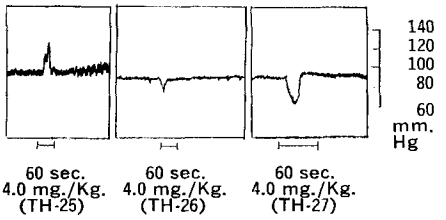


*Fig. 3—Rat blood pressure response to each of the cyclohexylamine hydrochloride salts (4.0 mg./Kg.).*

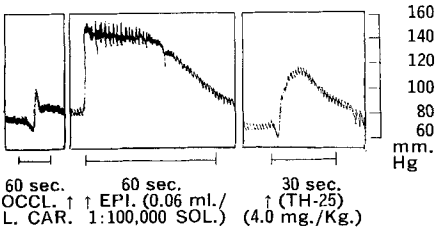


*Fig. 4—The effect of* trans-*2-*(p-*chlorophenyl*)-N,N-*dimethylcyclohexylamine hydrochloride (4.0 mg./Kg.) on rat blood pressure prior to hexamethonium (20 mg./Kg.).*

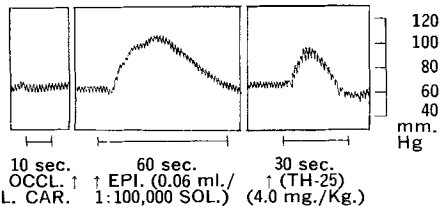


*Fig. 5—The effect of* trans-*2-*(p-*chlorophenyl*)-N,N-*dimethylcyclohexylamine hydrochloride (4.0 mg./Kg.) on rat blood pressure following hexamethonium (20 mg./Kg.).*

The effect of TH-25 on the rat blood pressure before and after i.v. hexamethonium is shown in Figs. 4 and 5. Prior to i.v. hexamethonium, occlusion of the left common carotid, epinephrine, and TH-25 each produced a transient pressor response of approximately 22%, 85%, and 60%, respectively.

Ten minutes after the slow i. v. injection of hexamethonium, occlusion of the left common carotid for 10 sec. failed to elicit the above-mentioned pressor response. However, second injections of epinephrine and TH-25 again produced transient pressor responses of approximately 60% and 42%, respectively.

The blood pressure results obtained with the nonethynyl cyclohexanol derivatives were typical of those previously obtained with other cyclohexanol derivatives (3). All produced an immediate transient drop in pressure. Although the magnitude of the effect was somewhat dose dependent, the duration of the effect was not. On the basis of the calculated $ED_{50}$ (Table I), CH-20 and CH-14 were equally effective in lowering rat blood pressure. Substitution of a hydroxyl group in both the 4 and the 5 position of the cyclohexanol ring (CH-21) decreased hypotensive activity approximately 30%. It is well known that the activity and toxicity of parent compounds tend to decrease upon the introduction of hydroxyl groups into a chemical structure.

The difference in the hypotensive activity of the cyclohexylamines studied appears to be attributed to both the spatial configuration of the compounds and to the number of methyl groups substituted on the amino nitrogen. In the *trans* configuration, the secondary amine (TH-26) possessed hypotensive activity, while the tertiary amine in the *trans* configuration (TH-25), was the only compound studied that possessed pressor activity. Moreover, in the *cis* configuration, the tertiary amine (TH-27) was approximately twice as active as the secondary amine (TH-26).

Pressor activity of cyclohexylalkylamines has been reported to be due to a direct increase in peripheral vascoconstrictor activity (7, 8). In the preliminary investigation of the mechanism involved in the pressor response to TH-25, reflex vasoconstriction *via* baroreceptor activity was not demonstrated. Moreover, depletion of catecholamine stores by reserpine does not alter the pressor activity (9). Again, the compound appears to be acting directly on the peripheral vasculature.

Thus, with the exception of TH-25 and the ethynyl derivatives of cyclohexanol, the rapid and transient hypotensive response of the compounds suggested direct myocardial depression.

**Isolated Guinea Pig Heart**—The results obtained in the isolated heart studies are shown in Table II. Recovery to 50% of the original amplitude level was also recorded, and varied with the type of compound studied. At the minimum effective dose, CH-20 and CH-14 had the shortest mean recovery time of 21 and 87 sec., respectively; TH-25, TH-26, and TH-27 possessed intermediate mean recovery times of 202, 868, and 1205, respectively; while the longest mean recovery time of 1280 sec. occurred with AH-65. Moreover, the heart arrested by AH-64 failed to show any signs of recovery and the experiments were terminated after a minimum of 3400 sec. of systolic standstill.

Table II—Comparison of the $ED_{95}$ (Cardio-Inhibitory) of the Cyclohexanol and Cyclohexylamine Derivatives on the Isolated Guinea Pig Heart

| Compd. | Total Trials | Calcd. $ED_{95}$, mg. |
|---|---|---|
| *trans*-2-*o*-Tolyl-*cis*-1,4-cyclohexanediol (CH-14) | 15 | 6.80 |
| *trans*-2-*o*-Tolyl-*trans*-1,5-cyclohexanediol (CH-20) | 8 | 3.38 |
| 1-Ethynyl-*trans*-2-*o*-tolylcyclohexanol (AH-64) | 11 | 2.52 |
| 1-Ethynyl-*cis*-2-*o*-tolylcyclohexanol (AH-65) | 10 | 1.33 |
| *trans*-2-(*p*-Chlorophenyl)-*N,N*-dimethylcyclohexylamine HCl (TH-25) | 9 | 0.78 |
| *trans*-2-(*p*-Chlorophenyl)-*N*-methylcyclohexylamine HCl (TH-26) | 8 | 1.19 |
| *cis*-2-(*p*-Chlorophenyl)-*N,N*-dimethylcyclohexylamine HCl (TH-27) | 10 | 0.85 |

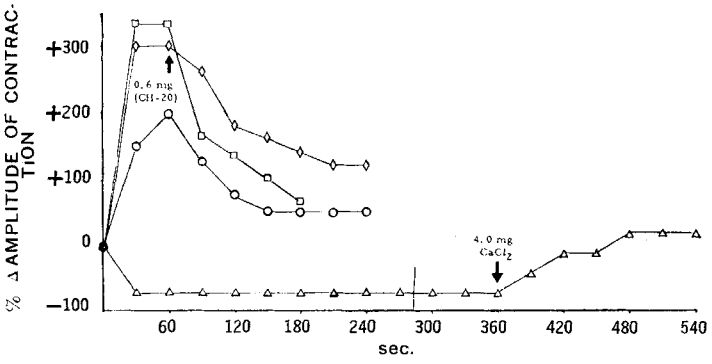


*Fig. 6—The effects of* trans-2-o-*tolyl* - trans - *1,5 - cyclohexanediol (0.6 mg.) and calcium chloride (4.0 mg.) on isolated rat atria. Key:* □, *4.0 mg.* $CaCl_2$; △, *0.6 mg. CH-20, followed by 4.0 mg.* $CaCl_2$; ◇, *4.0 mg.* $CaCl_2$, *followed by 0.6 mg. CH-20;* ○, *4.0 mg.* $CaCl_2$ *and 0.6 mg. CH-20.*

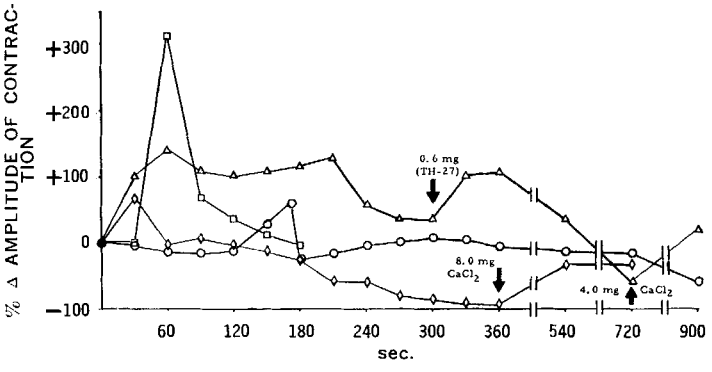


*Fig. 7—The effects of* cis-2-(p-*chlorophenyl*)-N,N - *dimethylcyclohexylamine hydrochloride (0.6 mg. and 1.2 mg.) and calcium chloride (4.0 mg. and 8.0 mg.) on isolated rat atria. Key:* □, *4.0 mg.* $CaCl_2$; △, *0.6 mg. TH-27, followed by 0.6 mg. TH-27 and 4.0 mg.* $CaCl_2$; ◇, *1.2 mg. TH-27, followed by 8.0 mg.* $CaCl_2$; ○, *1.2 mg. TH-27 and 8.0 mg.* $CaCl_2$.

A 1.0-mg. quantity of CH-21 produced a mean negative inotropic effect of 10%. Due to insufficient compound, the higher dosage levels could not be investigated.

The antagonistic effect of 8 and 16 mg. of calcium chloride on the cardiac arrest produced by 1.0 mg. of AH-65 was also noted. In all cases, calcium produced a transient positive inotropic response, proportional in duration and magnitude to the concentration of calcium used, and followed by the resumption of the pre-existing cardioplegia.

The primary purpose of the investigation was to determine whether the compounds possessed cardioinhibitory activity. The results in Table II show that the cyclohexylamine derivatives were up to 8 times more active in producing cardioplegia than were the derivatives of cyclohexanol. In the latter series of compounds, it appears that hydroxyl substitution at the 5 instead of the 4 position of the cyclohexanol ring increases activity 2 times. Moreover, when this hydroxyl substituent is omitted and an ethynyl group substituted at the 1 position of the cyclohexanol ring, activity increases 3 and 5 times with the *trans* and *cis* isomer, respectively. The *trans* isomer (AH-64) possessed cardiotoxic properties as the arrested hearts failed to recover spontaneously and remained in systolic standstill until the experiments were terminated at the end of 90 min. The *cis* isomer (AH-65) did not show any signs of cardiotoxicity at the dose levels employed.

It will be recalled that the tertiary cyclohexylamine in the *trans* configuration (TH-25) possessed pressor activity. Nevertheless, both TH-25 and TH-27 were equally potent and the most active of all the compounds studied in arresting the isolated guinea pig heart. Moreover, these two isomers were approximately 25% more active than TH-26 in producing cardioplegia.

**Isolated Rat Atria**—The results are shown in Figs. 6 and 7. The rate of the spontaneous beat of the preparation increased 17% when 4.0 mg. of calcium chloride alone was added to the bath, and was unchanged when 0.6 mg. of CH-20 preceded 4.0 mg. of calcium chloride. The rate increased 13% if calcium preceded CH-20 and increased only 7% when both were administered simultaneously.

Conversely, 0.6 mg. of TH-27 caused a 42% reduction in the rate of atrial contraction. Moreover, a second dose of 0.6 mg. of TH-27 when added to the bath at this point led to a final reduction in rate of 67%, which was unaltered by 4.0 mg. of calcium chloride. Likewise, 1.2 mg. of TH-27 added to the bath initially caused a 65% reduction in rate which was also unaltered by a subsequent dose of 8.0 mg. of calcium chloride. A 55% reduction in rate occurred when 1.2 mg. of TH-27 and 8.0 mg. of calcium chloride were added to the bath simultaneously.

*trans*-2-*o*-Tolylcyclohexanol has been reported to reduce the contraction amplitude of isolated rabbit atria without affecting the rate, and calcium to restore the amplitude to a normal level (3). In the present study, CH-20 similarly affected spontaneously beating rat atria, and calcium also restored the amplitude of contraction to a control level. TH-27 produced both negative inotropic and chronotropic effects on the isolated rat atria. A positive inotropic response, the duration of which was inversely proportional to the dose employed, preceded in all instances the negative inotropic effect. Calcium was able to restore the amplitude to control level, but unable to alter the negative chronotropic

response which progressed throughout the entire tissue exposure time. If given simultaneously with either CH-20 or TH-27, the onset of the negative inotropic effect was delayed by the calcium.

## SUMMARY AND CONCLUSIONS

As a group, the nonethynyl cyclohexanol derivatives were 2 to 7 times more potent than were the derivatives of cyclohexylamine in producing a hypotensive response in the intact rat. *trans*-2-*o*-Tolyl-*cis*-1,4-cyclohexanediol (CH-14) and *trans*-2-*o*-tolyl-*trans*-1,5-cyclohexanediol (CH-20) were equally effective and the most active, while the *trans* isomer of the tertiary cyclohexylamine (TH-25) was the least active and the only compound that produced a pressor response. The cyclohexylamine derivatives were up to 8 times more potent, in arresting the isolated guinea pig heart, than were the derivatives of cyclohexanol. The *trans* and *cis* isomers of the tertiary cyclohexylamine (TH-25 and TH-27) were equally effective and the most active; while *trans*-2-*o*-tolyl-*cis*-1,4-cyclohexanediol (CH-14) possessed the least amount of cardio-inhibitory activity among those compounds studied. An increase in the number of hydroxyl substituents on the cyclohexanol ring was accompanied by a decrease in both hypotensive and cardio-inhibitory activity. The minimum effective dose of 1-ethynyl-*trans*-2-*o*-tolylcyclohexanol (AH-64) in producing cardiac arrest was also the cardiotoxic dose; while the *cis* isomer (AH-65) showed the greatest cardio-inhibitory activity among the cyclohexanol derivatives studied. Spatial configuration was also significant in the blood pressure activity of the tertiary cyclohexylamines. The *cis* isomer (TH-27) produced a depressor response in contrast to the pressor response elicited by the *trans* isomer (TH-25). In the isolated atrial preparation, calcium antagonized the negative inotropic effects of *trans*-2-*o*-tolyl-*trans*-1,5-cyclohexanediol (CH-20) and *cis*-2-(*p*-chlorophenyl)-*N,N*-dimethylcyclohexylamine hydrochloride (TH-27). Moreover, calcium momentarily restored contraction of the heart arrested by 1-ethynyl-*cis*-2-*o*-tolylcyclohexanol (AH-65). In addition to its negative inotropic effect on the isolated atria, *cis*-2-(*p*-chlorophenyl)-*N,N*-dimethylcyclohexylamine hydrochloride (TH-27) also produced a negative chronotropic response which was unaffected by the administration of calcium. Decreased contraction of the myocardium appears to be responsible for the cardioplegia produced by the cyclohexanol compounds, since the pacemaker activity of the isolated atrial preparation is not affected. In addition to a decreased contraction of the myocardium, alteration of impulse formation or suppression of impulse conduction appear to be responsible for the cardioplegia produced by the cyclohexylamine derivatives. Preliminary studies of the pressor response to *trans*-2-(*p*-chlorophenyl)-*N,N*-dimethylcyclohexylamine hydrochloride (TH-25) indicate that the compound is capable of producing direct peripheral vasoconstriction.

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# Correlation of Dissolution Rate and Griseofulvin Absorption in Man

By B. KATCHEN and S. SYMCHOWICZ

**Five different griseofulvin preparations were studied in 10 healthy subjects. Plasma levels were followed for 24 hr. after single oral 500-mg. doses. The dissolution rate of each dosage form was measured in simulated intestinal fluid and distilled water. Good correlation was seen between dissolution rates in simulated intestinal fluid and griseofulvin absorption in man.**

GRISEOFULVIN is given in large amounts and is insoluble in water. Its dose in man is 125–500 mg., and its water solubility is 15 mcg./ml. at 37°. If the digestive fluids are saturated with respect to griseofulvin at all times, and griseofulvin solubility in digestive fluids is the same as in distilled water, a minimum of 33 L. of digestive fluids must be cleared for complete absorption of 500 mg. of griseofulvin as shown by the following calculation: dose (500 mg.)/solubility (15 mg./L.) = 33 L. Clearly, oral griseofulvin dosage

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