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Use of 1-(3', 4' dihydroxyphenyl)-2- isoprophylaminoethanol for the symptomatic relief of bronchia asthma

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THE USE OF 1-(3', 4' DIHYDROXYPHENYL)-2-ISOPROPYLAMINOETHANOL FOR THE SYMPTOMATIC RELIEF OF BRONCHIAL ASTHMA

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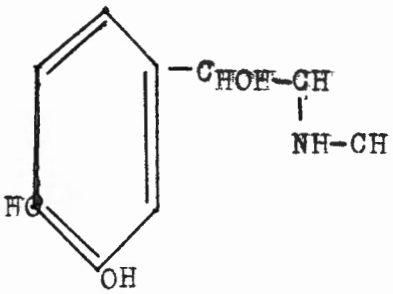
I Introduction

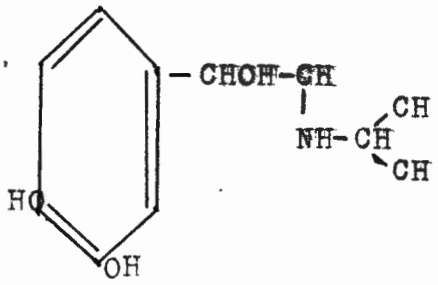
"Aleudrine" or 1-(3', 4'- Dehydroxyphenyl)-2- isopropylaminoethanol was first described by Konzett in 1940. He accurately determined the basic pharmacological properties of the drug. In 1945 Voegth and Verzar produced accurate data showing subjective and objective improvement of bronchospasm after inhalation of 1 per cent aleudrine. Since that time there have been numerous reports from both Europe and this country concerning the pharmacological and clinical aspects of this drug. The European literature speaks of the drug as "Aleudrin". In Britain it is known as "Neo-epinene". It is known as "Aludrine", or more commonly under the trade name of "Isuprel" (Winthrop-Stearns, Inc.) in the United States. Other trade names include "Isorenin" now "Isonorin" (Carroll Dunham Smith), I. P. A. (Specific Pharmaceuticals, Inc.) and Norisodrine (Abbott), the latter being the dust form. The drug may exist as the hydrocloride or sulfate salt.

II Chemistry

The official chemical name of Aludrine is isopropyl arterenol. It is the isopropyl derivitive of epinephrine. Its structural formula along with that for epinephrine is given below.



Epinephrine



Isopropyl arterenol

It is seen that the two formulae differ only by the presence of N-alkyl group.

The most significant pharmacological property of the drug is its bronchodilating action. The alteration of the structure of the molecule of epinephrine in relation to the ability of the new-formed drug to relieve bronchospasm has been extensively studied. Siegmunt (1) studied the bronchodilator effect of five homologues of epinephrine. These compounds differed in the N-alkyl group and the presence or absence of the hydroxyl group on the beta-carbon. Experimental asthma was produced in guinea pigs by the inhalation of a histamine solution as a finely dispersed mist. The animals were then injected intraperitoneally with the compound under test. Fifteen minutes later they were again exposed to the histamine. Records were made of the time

necessary to produce prominent symptoms or respiratory distress and the total time of exposure until asphyxial convulsions or collapse was produced. The results showed that Aludrine was the most effective bronchodilator in histamine-induced asthma, exceeding the activity of all other compounds. In the compound which had the same N-alkyl group as Aludrine, but contained a hydrogen instead of a hydroxyl group, the bronchodilating property was comparatively low. From the data gathered in this group of experiments it was shown that the alcoholic hydroxyl on the beta-carbon of the side chain, and an alkyl on the nitrogen, are important for bronchodilator activity of these compounds. The author speculated that since it had previously been shown that the N-n propyl homologue was very weak (Konzett) it was the branching of the chain that produced the pronounced increase in activity, in the case of Aludrine. He then infers that the N-alkyl group acts as a haptophore for a highly selective receptor mechanism. Compounds bearing groups that correspond closely to the optimal haptophore (in this case N-isopropyl) produce responses that are proportionate to their degree of similarity. This suggests there are definite structural requirements for bronchodilation comparable to those which have been described as essential for vasomotor effects.

Siegmunt (2) studied other analogs of Isuprel and found that Aludrine remained the most potent bronchodilator dnug in the intact animal, although the cyclopentyl analog was shown to possess a bronchodilator activity equal to or exceeding that of Aludrine in the perfused lung but

had only one-twentieth of the activity of the histamine-asthma test. The results of this study indicated that the increase in size of the N-alkyl group appears to decrease the bronchodilator effect. It also substantiated the earlier conclusion that the side chain contributes markedly to the activity.

The changes in the structural formula relative to toxicity was also studied by Siegmunt (1). The comparative toxicity of the compounds was determined by intraperitoneal injection into albino mice which were then observed for 72 hours. The toxicity of the N-isopropyl homologue (Isuprel) was slightly greater than that of the N-sec. butyl and the ethane derivitives. All three of these compounds are remarkably low in toxicity but it can be seen that toxicity does not correspond directly with bronchelytic activity. The author points out that the important factor for the low toxicity probably lies in the branching of the alkyl group attached to the nitrogen.

III Pharmacology

The pharmacology of Aludrine was first worked out by Konzett in 1940. Segal (3) was the first in this country to study the pharmacological and clinical aspects of the drug. He showed that in humans bronchospasm was relieved and there was an improvement in vital capacity, that fluctuations in blood pressure were abolished or decreased, and that presser effects and tachycardia were minimal. His studies were carried out on asthmatics receiving the drug by one or a combination of three routes. 187 trials were carried out in 82 ambulatory and 40 hospitalized patients.

A. Bronchodilating effect

Lands (4) studied the effectiveness of Aludrine in preventing vasoconstriction in experimentally produced asthma in guinea pigs. The animals were confined to a glass container and exposed to an 0.2 per cent solution of histamine diphosphate in the form of a finely nebulized mist. Data were tabulated under "onset" or the time the guinea pigs were subjected to the histamine mist until obvious symptoms of asthma were noted, and "duration" or the time elapsing between the beginning of the exposure and time of collapse or asphyxial convulsions. Doses as small as 0.025 mgm./kgm of Isuprel caused a significant prolongation in the time of onset of asphyxial signs and diminished the severity of histamine shock.

Lands (4) perfused isolated guinea pig lungs first with histamine acid phosphate and then one of the bronchodilator compounds. Aludrine was as effective as epinephrine. Cohen (5) studied the effects of

Aludrine in dogs under anesthesia. The animals were anesthetized with a pentothal-curare mixture, an endothracheal tube inserted; a mixture of 500 cc oxygen and 500 cc nitrous oxide was then given. A bronchoscope was inserted through which a small catheter with an attached cuff was introduced. A larger bore tube with an inflatable cuff was then introduced into the trachea after the bronchoscope was removed. This allowed the endobronchial catheter to lie alongside the tracheal catheter in the trachea and to emerge to the outside. The inflatable cuffs were connected to water manometers and expanded to positive pressures. Changes in the bronchi and trachea were thereby redorded. The effectiveness of Aludrine as a bronchodilator was shown as well as the minimal effect on the cardiovascular system as compared to epinephrine, benadryl, ephedrine, and amenophylline.

Konzett (6) demonstrated that the bronchodilator action of Aludrine as compared to epinephrine was 10:1. Experiments were carried out on isolated dogs lungs perfused with blood. Aludrine caused bronchodilation when given in doses of one microgram and upwards. This was observed in untreated lungs in which bronchoconstriction had already been induced by injection either of histamine or of parasympathetic drugs, including pitocarpine and acetylcholine. When the bronchodilator actions of Aludrine and epinephrine were compared during the first one to two hours of perfusion it was found that Aludrine had the greater activity; to produce an identical response the dose of isuprel required was as little as one-tenth the dose of epinephrine. The stronger bronchodilator action of Aludrine could also be inferred from the fact that preparations which

were insensitive to epinephrine (10 microgm.) nevertheless responded to Aludrine (1 microgm.) when perfusion was prolonged for more than one to two hours, epinephrine quite frequently produced a diphasic response in which bronchoconstriction, following a brief bronchodilatation, predominated. Even under these conditions, Aludrine had a powerful bronchodilator action. Unlike epinephrine, Aludrine did not show any evidence of bronchoconstriction in any of the experiments. The difference in activity of the two drugs is even greater than 10:1 if allowance is made for the higher molecular weight of Aludrine. Konzett believes that the results obtained by Aludrine in comparison to epinephrine for the relief of bronchospasm in the dog perfusion experiments more nearly parallels the clinical experience of the drug. He suggests that dog lungs thereby provide a more reliable means for the assay of bronchomotor drugs than do perfused guinea pig lungs.

B. Effects of Aludrine on the cardiovascular system

1. Blood pressure

Lands (4) in experiments on dogs anesthetized with sodium pentobarbital studied the effects of Aludrine on blood pressure. Intravenous injections of Aludrine in doses of one to two micrograms per kgm caused a marked fall in the carotid blood pressure. Direct comparison indicated that this fall was of somewhat greater magnitude and duration than the rise in blood pressure obtained with an equal dose of epinephrine.

He demonstrated, on the other hand, that when unanesthetized dogs were given Aludrine, there was a rise in systolic pressure in spite of

evidence of peripheral vasodilatation. Since a marked tachycardia was observed it was thought that this initial rise in systolic pressure resulted from an increased cardiac action. As the cardiac effect of the drug diminished, the blood pressure returned to normal, and in most experiments, continued to decline to levels distinctly below those of the control period. This effect was quite prolonged.

Cohen (5) in experiments on anesthetized dogs showed that the blood pressure as recorded on a kymograph from a cannulated carotid artery was not particularly altered when Aludrine was given in dosages of 0.001 mg/kgm. However, he showed that large doses of Aludrine caused a reduction in blood pressure to within 40% of normal but the blood pressure returned to normal levels in 45 minutes to one hour.

Lands (4) demonstrated that the vasodepressor action of Aludrine was reversed to vasopressor action by small doses of ergotamine or ergotoxine. This reversal was associated with a marked increase in the amplitude of ventricular contraction, in pulse pressure and rate. The effect produced here seemed to be the result of an increase in cardiac output into a vascular bed which had been thrown into a sustained state of vasoconstriction by the reversing drug.

Konzett (6) was the first to experiment on the effects of Aludrine on the pulmonary circulation. Studies were carried out on the isolated dog lungs perfused with blood. Continuous records were made of the pulmonary artery pressure and the venous reservoir volume. Doses of 1 microgm or more of Aludrine caused a slow but definite fall in pulmonary

arterial pressure. The decrease in resistance was somewhat accompanied by a fall in the venous reservoir volume indicating an increase in capacity of the blood vessels, but this response was not so regularly observed. These responses were in striking contrast to those of epinephrine which over a wide range of doses (1 to 100 micrograms.) always produced a rise in the pulmonary arterial pressure and a fall in lung blood volume.

It was therefore shown that Aludrine has a pulmonary vasodilator action in anesthetized dogs but whether this is true for the unanesthetized animal couldnot be ascertained. If it is true this diminished resistance in the pulmonary vascular blood would reduce the load on the right heart. This diminished resistance with the improvement of blood flow through the lungs may be responsible for the antidyspnic effect of Aludrine as the bronchodilator effect of the drug. Both actions should improve the conditions of gas exchanges in the alveoli. It is interesting to note in this connection that the beneficial effect of aminophylline, especially in epinephrine-resistant asthmatics, has been attributed to its pulmonary vascular action rather than its relatively weak bronchodilator properties.

2. Effect on heart

Lands (4) studied the cardiac effects of Aludrine on isolated perfused hearts of frogs and of rabbits. Five to 10 micrograms of Aludrine increased heart action in frogs. The effects were more prolonged than those caused by epinephrine. However, one difference in response was noted: with an injection of 10 micrograms or more of epinephrine

the heart was brought to diastolic standstill, whereas with an equivalent amount of Aludrine no such effect was observed. The perfusion of an isolated rabbit heart with 0.2 to 2.0 micrograms of Aludrine stimulates the heart, increasing both rate and amplitude.

On a few experiments with dogs myocardiographic recordings of the left ventricle were made by Lands (4). Aludrine caused a prompt increase in both rate and amplitude in the absence of blood pressure changes and these changes lasted for approximately twenty minutes.

Cohen (5) observed by direct vision changes in the lumen of the coronaries when Aludrine was given. Dogs anesthetized by a pentothal-curare mixture plus nitrous oxide and oxygen had their pericardia incised so as to expose the heart and coronary vessels. A one per cent solution of procaine was sprayed into the surrounding areas to prevent cardiac irregularities. When a therapeutic dose of Aludrine was given to the animal, no gross change was apparent in the diameter of the coronary arteries. When larger doses of Aludrine were given (0.75 mg. per kgm.) the heart was observed to increase rapidly in rate and force of beat; the coronary vessels appeared to dilate about 50%, and the veins became fuller and congested. As a comparative study, aminophylline (7.5 mg. per kgm.) was given. Marked dilatation occurred in these situations.

Nathanson (8) studied the effect of Aludrine on the rhythmic property of the human heart. This was carried out by observing the effect of Aludrine on fourteen patients with induced cardiac standstill and five patients with complete heart block. Electrocardiograms were made

showing the cardiac standstill induced by the carotid sinus compression. Aludrine was administered subcutaneously in doses of 0.14 to 0.2 mg. and electrocardiogram tracings were made at regular intervals. The cardiac inhibition induced by the carotid sinus pressure was abolished in every instance following the administration of Aludrine. This effect was noted five minutes after the injection of the drug. The standstill was abolished by the restoration of the activity of the sinus node or by the initiation of ectopic auricular or ventricular pacemakers. In some instances multiple rhythmic foci were induced by the drug.

Another method of study of the action of Aludrine on the heart was the use of the drug on patients with complete heart block. An increase in ventricular rate is an indication of the effectiveness of a sympathomimetic drug on the rhythmic function of the ventricular pacemaker. After a control electrocardiogram was made, 0.2 mg. Aludrine was administrated subcutaneously to five patients with complete heart block. Electrocardiograms were made at regular intervals for one to two hours. There was a definite increase in ventricular rate in every instance.

These observations indicate that a pressor action is not essential for the production of epinephrine-like effect on the heart. The possible clinical value of this effect of Aludrine will be commented on later. The author in comparing the results of this study on carotid sinus induced cardiac standstill with previous observations in which epinephrine was used, it appeared that the pacemaker induced by Aludrine was usually in the sinus node, in lower auricular foci or in the auricular-ventricular node. There was seldom an excitation of lower ventricular foci. In

contrast, epinephrine frequently induced rhythmic foci from lower ventricular centers, and at times multifocal ectopic ventricular beats resembling a pre-fibrillation rhythm occured.

Garb (9) studied the effect of Aludrine along with two other sympathomimetic amines (including epinephrine) on the contractility of the heart muscle. He used a papillary muscle preparation consisting of the chorda tendina of an isolated muscle attached to a string gauge. The muscle was immersed in oxygenated Locke's solution and was stimulated electrically. After equilibration, the contractile force was measured and the drug added to the solution. The contractile force was again measured. All the drugs studied produced an increase in the force of contraction of each muscle. There was considerable variation in the degree of the increase, so that accurate quantitative relationships between the drugs could not be derived from this study. However, it was demonstrated that Aludrine has contractile-producing action on mammalian heart muscle which is at least as great as that produced by epinephrine.

Gay (10) in his comprehensive evaluation of Aludrine conducted electrocardiogram studies on six patients before and after administration of 0.1 cc of a 1:1000 solution of the drug. A review of changes listed in four of these tracings showed that all had sufficient positive findings for the demonstration of coronary insufficiency. Such changes occured in one patient without significant coincident increase in heart rate. He concluded that Aludrine overdosage was of great potential danger in a patient whose myocardium might be partially anoxic by virtue of an

attack of bronchial asthma. However, he was of the opinion that the action of Aludrine in these observations was not one of coronary artery constriction but of the decided increase in the force of myocardial contraction and a resulting demand for more oxygen, which of course is not met.

Lettman (11) has so far to date most exhaustively studied the electrocardiogram changes produced by Aludrine. He has shown that there is a definite pattern of electrocardiogram changes produced by the drug but that these electrocardiogram abnormalities are not due to tachycardia or hypotension but appear to be due to myocardial action of the drug. The characteristic electrocardiogram changes consisted of the following:

1. Sinus tachycardia (in all cases)
2. Depression of the s - t junction (most striking abnormality)
3. A trough-like configuration (suggested augmentation of the auricular T waves.)
4. Increase in amplitude of the T waves in the chest leads (often seen).

In a few instances there was wandering of the pacemaker, both within the sinus node and to the A-V node, associated with ventricular premature contractions, sometimes in beginning or trigenning.

Lettman then attempted to discover the genesis of the electrocardiogram changes. To do this he had to use a drug which would overcome the vasodepressor effect and rate-stimulating effect of Aludrine without creating an electrocardiogram pattern of its own. Arterenol was selected because when used alone it caused a rise in systolic and diastolic blood

pressure without producing electrocardiogram changes except bradycardia. 0.25 mg. of Aludrine subcutaneously was administered to normal young adults. After the maximum effect was obtained, arterenol was given. Complete reversal of certain of the isopropyl effects resulted: systolic and diastolic blood pressures began to rise, rapidly exceeding the control levels and there was a diminution of the tachycardia, the rate becoming stabilized slightly above the control level. However, the electrocardiogram abnormalities induced by Aludrine subsided only slightly with the disappearance of the tachycardia and with the change in diastolic blood pressure from severe hypotensive to slight hypertensive levels. The depression of the S - T junction persisted in all leads for an hour after the arterenol injection, with only a slight diminution of this deviation incident to the marked changes in the blood pressure and rate. These experiments rule out changes in blood pressure and tachycardia as a cause of electrocardiogram changes.

C. Other effects (effects on other tissues and organs)

1. Effect on intestine

Lands (4) showed that Aludrine in a dilution of one part in 10 to 40 million caused a reduction in tonus and motility on segments of the guinea pig ileum. Epinephrine gave comparable results in these dilutions, but concentrations as great as one part in two million caused a strong contraction rather than relaxation. At this concentration Aludrine caused only relaxation. This inhibitory action on the intestine was demonstrated only on the organ in situ. Doses of Aludrine of 0.05 to

0.30 mgm/kgm caused a prompt reduction in tonus and motility on the rabbit small intestine and colon.

2. Effect on uterus

The effect of Aludrine on the uterus was studied by Lands (4) in a way similar to the method used on the intestine. Aludrine in high dilution caused inhibition of motility on both the isolated non-gravid uteri of the rabbit and guinea pig. By comparison epinephrine in these dilutions caused only stimulation.

3. Effect on mucous membranes

Herxheimer (12) studied the effects of Aludrine on the mucous membranes of rabbits. Twelve animals inhaled aerosol of Aludrine of a 0.25% solution ten minutes each day for 30 days. They were then sacrificed, the trachea excised. A drop of india ink was dropped on the mucous membrane and its movement watched. Following this sections were prepared for histological study. This investigator concluded that Aludrine in therapeutic concentrations is not harmful to the mucosa of rabbits. Whether adrenaline produced harmful results remains an open question.

4. Effect on blood sugar and glucose tolerance

Gay (10) showed that there was no constant or significant change in blood sugar concentration in six patients tested before and 15 minutes after injection of 0.3 cc 1:5000 Aludrine.

Ingle (13) studied the effects of Aludrine on glucose tolerance of rats. Eviserated rats were given continous intravenous infusions of glucose and insulin during a period of two hours. The glucose load was

64 mg. of glucose per 100 gm. of rat per hour and insulin was given at the rate of 4 units per rat per 24 hours. The solution of glucose and insulin was infused at the rate of 20 cc. per 24 hours. The addition of Aludrine in concentrations of 1:10,000 and 1:25,000 caused a marked decrease in the glucose tolerance of the eviscerated rats. The author suggested that changes may be secondary to circulatory changes e.g. vasodilation.

5. Blood morphology

Gay (10) studied the blood morphology of ten asthmatic patients prior and following (periods of four weeks to three months) Aludrine administration. He found no significant alterations in any case.

Cavanna(14) also stated that therapeutic doses of Aludrine do not influence the blood count.

Apparently there is no change in circulating eosinophils.

Segal (17) stated that the sympathetic amines elicit body responses which simulate those resulting from stimulation of adenergic nerves, but the location and intensities of the responses differ widely.

Konzett (Lands (4)) suggested that the effects of Aludrine on the bronchial musculature, coronary vessels, intestine, and uterus might be expected to result from a suppression of the excitatory (sympathin E) effects of epinephrine or to result from a modification of the molecular structure of epinephrine so that specific stimulation of the depressor mechanism results. However, the stimulating effect on the heart would seem to be an exception to the postulation that sympathetic inhibition

leads to the liberation of a substance into the blood stream causing inhibitory effects on other sympathetically innervated structures similarly affected by epinephrine.

Hebb and Konzett (6) stated that sincecardiac action and the increase in blood sugar, Aludrine should be regarded as having predominantly inhibitory epinephrine-like actions without being altogether devoid of excitatory properties. It is interesting to note that the vasodepressor effect of both epinephrine and Aludrine can be reversed by parasympathetic substances e.g. pitocarpine and can later be restored when atropine is given. It appears that both epinephrine and Aludrine are amphotropic substances with inhibitory and excitatory properties. The fact that the direction of response can be varied might be attributed either to changes in the sensitivity of any group of receptor cells or to unmasking of other receptor cells.

D. Toxicity

Siegmunt (1) demonstrated that only two other homologues of epinephrine other than Aludrine had less toxicity than Aludrine. The L D_{50} of these were 480 and 490 mgm/kgm as compared to 450 mg/kgm for Aludrine. The epinephrine ratio for Aludrine (standard for bronchodilator activity) was over twice that of either of these compounds, however. These studies on comparative toxicity were carried out by injecting albino mice intraperitoneally with the drug under study; the animals were observed 72 hours following the injection.

Lands (4) determined the acute toxicity in albino mice by intraperitoneal injection. The L D_{50} for Aludrine was 450 as compared to a

L D_{50} for epinephrine of 4.

Dertinger (15) extensively studied the toxicity of Aludrine on several mammalian species. Aludrine was shown to have a low acute toxicity in mice. Epinephrine is about 24 (intravenous) to 107 (intraperitoneal) times more toxic. The intravenous L D50 for mice is 494 mg/kgm. Intravenous injection in rabbits (35 to 60 mg/kgm) caused some deaths at all doses. Among rats receiving subcutaneous injections of 100 mg/kgm daily for five days there were no deaths. Dogs were more sensitive; 15 mg/kgm caused death in one case when administered orally, although some animals survived doses of 50 mg/kgm. Dogs fed 5 mg/kgm for six to seventeen weeks showed a good tolerance. Aludrine did not interfere with growth of weanling rats when incorporated in the diet at a level of five per cent by weight.

Cohen (5) studied the toxic effects of Aludrine in anesthetized dogs. Aludrine was given intravenously to a 15 kgm dog until a total dosage of 61.36 mg was given within a fourteen minute period. A marked tachycardia of 230 beats per minute developed and the blood pressure reading fell 62 mm systolic and 56 mm diastolic. Even with this large dose, 4086 times the therapeutic intravenous dose, he was unable to lower the blood pressure past that level. The only changes in the recording of the electrocardiogram were extreme tachycardia, S - T depression, and an inverted or diphasic T wave. The last two changes were interpreted as coronary insufficiency secondary to the extreme heart rate. After one hour the animal's pressure had returned to normal levels even though its heart rate was still rapid. Further experiments by Cohen (5) to determine

the toxic dose for animals under anesthesia revealed that all animals tested were able to tolerate at least 1 mg of Aludrine per kgm given intravenously.

Cohen stated that the toxic dose in dogs calculated to the human scale is 2,500 times the therapeutic dose.

IV Clinical response of asthmatic patients to drug

Clinical effects of anti-asthmatic drugs are difficult to evaluate. Innumerable drugs have been warmly recommended, and often a high percentage of "cures" have been claimed. Many of these observations, however, depend only on reports by patients, and asthmatic patients tend to be very suggestible. Herxheimer (12) states that if one is to rely on patients' reports, the patients should be tested for reliability beforehand. Only if they report correctly on the absence of effects after tablets or inhalants known to be ineffective, and only if they have considerable experience in the variability of their own attacks, can they be regarded as reliable.

Herxheimer goes on to emphasize that the only practicable objective measurement is the vital capacity, which is very sensitive to bronchial spasm. Even here there are sources of error. For instance, the degree of bronchospasm is not constant, and the stronger the spasm the greater is the relief of the antispasmodic drug. If the spasm is very slight and the vital capacity is reduced only a little, the same amount of drug may have no effect or a very small one. There can, therefore, be no constant condition as a basis for the investigation. Another disadvantage is that emotional factors may influence the bronchospasm at the same time. In suggestible patients the initial action of an effective antispasmodic restores confidence and this may cut short the attack. This confidence sometimes enhances, or even doubles, the antispasmodic action of the drug.

After Konzett demonstrated that Aludrine was ten times more effective

than epinephrine in abolishing bronchoconstriction in dogs, other European investigators set out to note the effects of the drug for the relief of bronchospasm in asthmatics. Dautrebande using the aerosol technique in the treatment of bronchial asthma stated that up to five or ten inspirations of a 1:1,000 solution of Aludrine produced sustained bronchodilation without alarming side effects. Stolzenberger-Seidel, using a 1:100 solution of Aludrine reported very favorable results in 100 cases. He stated that the full relief of the asthmatic paroxysms was obtained within two to five minutes. Where this drug had been used for one year or longer, there has been no evidence of diminution in effectiveness.

Quitchal reported the successful treatment of 148 asthmoidal conditions arising from chronic bronchitis and emphysema with Aludrine. A 1% solution of the drug was inhaled in his series of cases. In many instances liquefaction and expectoration were facilitated by the use of this drug. There was a remarkable increase in the vital capacity of patients with emphysema. The technique used in this study was to have the patient inhale the 1% Aludrine solution three times on day, taking fifteen inspirations each time. No addition to the drug was observed. In this study only five of 148 patients recorded cardiac palpitation which disappeared five minutes following inhalation.

Segal published the first report in the United States on Aludrine. He showed that the subjective relief of bronchospasm was correlated with improvement in vital capacity and the greater the degree of bronchospasm, the greater the improvement in vital capacity. Undesirable pressor effects and

and tachycardia were minimal and greatly corresponded to the individual's tolerance to sympathomimetic amines. In a second report (3) which included further observations on his 187 trials in 82 ambulatory and 40 hospitalized patients he noted that the fluctuations in blood pressure observed in asthmatics (variation in systolic and diastolic readings in inspiration and expiration) were effectively abolished or markedly decreased and in an especially dramatic fashion when the bronchospasm was greatest. He also demonstrated that the epinephrine-fast state observed in eleven patients responded favorably to Aludrine and that no fastness to Aludrine could be observed. He used three routes of administration for the drug and determined the advantages and disadvantages of these various routes as well as the optimal dosages.

Herxheimer (16) showed that the dosage of the drug varied widely. On the whole the younger the patient and the shorter the history, the smaller the dose needed. A middleaged patient with a short history will probably require less than a young one with a long history. Elderly emphysematous patients nearly always require higher doses.

1. Oral

Segal (3) in his clinical study of the effect of Aludrine administered by various routes felt that the drug taken orally was not as effective as inhalation. The action was too slow to warrant its use in the acute stage of asthma. He believed, however, that it may have a place in the management of the chronic asthmatic who wheezes some every day but rarely has a severe attack. In his studies he used 5 to 10 mg every

three to six hours which amounted to 30 to 60 mg per day.

Gay (10) emphasized the wide variation in both therapeutic response and incidence of side reactions when Aludrine was given orally. With doses of 25 mg or more the majority of his patients (80% of 30 patients) experienced side actions of a severe and disagreeable nature sufficient to render use of the drug in such dosage impractical. Of the patients in this group experiencing mild asthma 75% reported moderate to marked relief with doses of either 25 or 50 mg. The larger dose produced side effects by greater intensity and duration without the significant increase in the degree of relief afforded. Of the patients experiencing paroxysms of severe asthma only 25% reported significant benefit with doses of either 25 or 50 mg.

Because of the severe and disagreeable side reactions produced by a dosage of 25 mg, further investigations were carried out with a reduced dosage of 15 mg. 75% of 36 patients who received 15 mg of Aludrine reported some side effect with this dosage. However, the side actions were mild and fleeting in nature and in only one instance of a severity great enough to prohibit use of the drug. 83% of all patients with mild asthma reported moderate to marked relief following 15 mg taken at the onset of the attack. Those patients who allowed their asthma to go unabated and those experiencing severe asthma after onset failed to obtain significant benefit from 15 mg and had to resort to other therapy.

Because of lag from time of administration to effects could be noted, the high incidence of severe and disagreeable side reactions, and the

dubious value in the alleviation of the severe attack, this form of administration was early supplanted by other methods.

2. Sublingual

Lipman (1949) was the first investigator to use the sublingual route of administration of Aludrine. He treated all of his 23 patients with 5 mg tablets held beneath the tongue when the first signs of asthma were noted. Half of these patients (12) were completely relieved of one or more attacks within five to thirty minutes by one tablet. A third (8) received only partial or slight relief from the sublingual tablet and required one or more doses of the subcutaneous injections for complete relief. Of the 23 patients, 14 had side reactions ranging from mild palpitation to severe palpitation, weakness, and nausea. He concluded that Aludrine sublingually was a good adjunct in the treatment of the dyspnea of bronchial asthma although side reactions are common with its use. However, he believed the subcutaneous route to be superior.

Gay (10) concluded that sublingual absorption of 10 mg pellets of Aludrine was the second method of choice for the relief of bronchospasm (inhalation being the first). This was true, he believed, because of its convenience, speed of action, and the fact that the patient can discard all undissolved drug in the event of serious side effects. The sublingual was of the greatest value in the early abortion of mild asthma. It was of less value in moderate asthma and of no benefit in severe asthma. It caused mild and fleeting side action in 33% of the users. His study was carried out by repeated trials on 47 patients. Each was instructed

to place one tablet beneath the tongue the moment he was aware of an attack coming on, and to allow it to dissolve there without swallowing. If no benefit or ill effect was apparent in 15 minutes a second "sublinguet" was to be used, and after another interval of 15 minutes, a third tablet could be tried. In these trials the patient was given Aludrine for two weeks followed by a placebo for two weeks after which Aludrine was continued. Only one patient in 25 with mild asthma failed to obtain relief using the sublinguet as instructed. The majority (21 out of 25) could completely abort the attack with the use of one sublinguet if taken promptly at the onset of wheezing. If the patient allowed his asthma to increase in severity and become fully established, relief afforded by the linguet taken then was proportionately less and other treatment had to be used.

In those patients benefited, relief was generally felt in three to five minutes and lasted from one to four hours. In many instances of mild asthma the patient could report complete relief with one or two sublinguets and no return of symptoms for 24 hours or more. About one-third of all patients using sublinguet reported palpitation of a mild fleeting nature, in no instance distressing enough to withhold the drug. Of the 47 patients treated, two had precordial pain, 3 had headache, 2 nausea, and 1, nervousness.

An interesting part of Gay's report was of the patients' choice of an antiasthmatic tablet consisting of aminophylline, phenobarbital, and ephedrine over Aludrine. The patients choose this antiasthmatic tablet

three to one over Aludrine because it relieved asthma of severity, had greater duration of relief and had relative absence of unpleasant side effects. All agreed, however, that the linguet afforded the quickest relief and that its greatest usefulness was in the prompt abortion of asthma of mild degree.

Other investigators have concluded as did Gay that the sublingual administration of Aludrine may be of some value in the treatment of mild attacks of bronchial asthma. However, it has no particular advantage over the inhalation method to be discussed later, and has several disadvantages over this method.

3. Subcutaneous administration

Segal (3) showed that when Aludrine was given subcutaneously, the dosage of 0.25 cc of a 1:1000 dilution gave the best relief with the least side effects. In his series, a marked and immediate relief was noted; in five minutes there was a noticeable relief and in ten minutes the peak of the response was observed. There was an average increase in V. C. of 1.4 L. The effect, however, was not of long duration; the patients required another injection in two to three hours to maintain initial improvement. He believed that the greatest effect was the breaking up of the cycle of status asthmaticus although intensive therapy over the following 12 to 24 hours had to be given to retain gains made. He concluded that the 1:1000 dilution of Aludrine given subcutaneously was most effective in the initial active treatment of the very ill asthmatic who needs hospitalization.

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3. Subcutaneous

Segal (3) showed that when Aludrine was given subcutaneously, the dosage of 0.25 cc of a 1:1,000 dilution gave the best relief with the least side effects. In his series, a marked and immediate relief was noted; in five minutes there was a noticeable relief and in ten minutes the peak of the response was observed. There was an average increase in vital capacity of 1.4 liters. The effect, however, was not of long duration; the patients required another injection in two to three hours to maintain initial improvement. He believed that the greatest effect was the breaking up of the cycle of status asthmaticus although intensive therapy over the following 12 to 24 hours had to be given to retain gains made. He concluded that the 1:1,000 dilution of Aludrine given subcutaneously was most effective in the initial active treatment of the very ill asthmatic who needs hospitalization.

Lipman (18) pointed out that of his 23 patients treated, 8 received

only partial or slight relief from the sublingual tablet and required one or more doses of the subcutaneous injections for complete relief. Aludrine subcutaneously proved to him to be the most valuable drug of the drugs tested (ephedrine, aminophylline, and epinephrine) and the method used (sublingual, oral, or subcutaneous) because its action was comparable to that of epinephrine and because it relieved the so-called epinephrine-resistant types of dyspnea. Its side reactions were not as severe as the side reactions of epinephrine.

Gay (10) in his study of ten patients during paroxysms of severe bronchial asthma demonstrated that although in eight patients there was a prompt and pronounced benefit when Aludrine 1:1000 dilution in dosages of 0.1 to 0.5 cc was given, each patient experienced side effects of moderate to marked degree--in some instances sufficiently alarming to preclude the continued use of the drug in this strength. All injections thereafter were of a 1:5,000 dilution with doses varying from 0.3 to 0.5 cc and repeated as warranted. Of 16 patients with mild episodes of asthma given 0.3 cc, every patient received prompt and definite relief, generally a complete abolition of the wheezing state. Of 16 patients with asthma of moderate severity given 0.3 to 0.5 cc, 10 obtained decided relief, 4 slight relief, and 2, no relief. Of 9 patients with severe prolonged asthma given 0.3 to 0.5 cc, 4 obtained significant benefit with a second dose after fifteen minutes and 5 obtained no help. Of all these 41 patients, only 17 (41%) experienced side effects, and in no instance were these of a nature or degree sufficient to render the dosage unsafe

or impractical. It is interesting to note that Aludrine 1:5,000 of a dosage of 0.3 to 0.5 cc subcutaneously was determined by Gay to be equivalent to 0.3 to 0.5 cc of epinephrine 1:1,000 given intramuscularly. He concluded, however, that Aludrine was not found to be significantly superior to epinephrine for use by injection. On five occasions he obtained favorable responses from epinephrine-fast patients, and therefore believes that a trial of Aludrine 0.3 cc to 0.5 cc of 1:5,000 is indicated in any patient in the epinephrine-fast state. This plus the fact that Aludrine appeared to have a slightly more rapid onset of action were the only advantages that Aludrine could offer over epinephrine.

Gay demonstrated that Aludrine in dilution of 1:1,000 given in dosages of 0.1 to 0.5 cc produced marked tachycardia and increase in pulse pressure, with moderate rise in systolic and fall in diastolic levels. He also demonstrated electrocardiogram pattern changes (evidence of coronary insufficiency) when Aludrine of 1:1,000 concentration subcutaneously was administered. He therefore advised the use of Aludrine 0.3 cc to 0.5 cc in 1:5,000 dilution as a safe and practical method of administration in selected patients as opposed to the concentration and dosage prescribed by Segal. Gay, contrary to Lipman's opinion, thought that Aludrine subcutaneously was not significantly superior to epinephrine subcutaneously even though Aludrine was successful in the treatment of patients with epinephrine-fast asthma. He demonstrated in his series of 41 patients that when the concentration of Aludrine was reduced to minimize the side effects that in many instances were marked, the effects

of the drug diminished as the severity of the asthma increased. This would seem to negate Segal's observation that subcutaneously given Aludrine would be most effective in the very ill asthmatic (except, of course, if the patient were epinephrine-fast). The electrocardiogram changes as noted by Gay were probably not due to the direct effect of the drug on the coronary arteries. It seems probable that they were associated with tachycardia and increased demands put on a somewhat already anoxic heart due to reduced oxygenation of blood of a patient with pulmonary disease.

4. Intravenous administration

This route of administration has not been investigated to the degree the other routes have. Segal (3) stated that the drug should not be given intravenously. The rapid effect of the drug given via the various other routes has made experimentation of the intravenous administration route unnecessary. Cohen (5) however, in his experiments on anesthetized dogs used Aludrine intravenously. It was necessary to give all drugs intravenously since this is the route most accessible to the anesthesiologist who needs both an immediate and full response.

The use of Aludrine to solve the problem of bronchospasm induced under anesthesia has been associated with the intravenous use of this drug. Cohen (5) reports seven clinical cases of bronchospasm occuring during anesthesia in which Aludrine was used. In all cases complete relief was obtained throughout the surgical and immediate postoperative periods. Rises in pulse rate and blood pressure were minimal in all patients. The largest total dose of Aludrine was 0.068 mg. Bronchospasm presents a

definite problem in anesthesia, and asthmatics in particular frequently are difficult to anesthetize. Many patients who have no past history of allergy first develop evidence of asthma under anesthesia. The converse of this is also true. Baird's pentothal-curare anesthesia has proved to be an excellent anesthesia for all types of patients and operations. The combined parasympathomimetic effects of pentothal and the histamine release action of curare, however, make its use somewhat hazardous in asthmatics. A safe drug that would relieve bronchospasm and still not produce cardiovascular side effects would remove an important contraindication to its use.

Other uses of the drug such as treatment of sudden cardiac failure which occurs in heart block may be associated with intravenous or perhaps intracardial administration.

5. Inhalation

Inhalation of the drug was used by the earliest investigators of Aludrine and the benefits derived have established inhalation as the most desirable method of administration particularly since the development of inhalation of the drug in the form of a dust. Segal (3) pointed out the advantage of inhalation was due to the tremendous absorptive powers of the inner surface of the lung whereby an inhaled medicament almost immediately reaches the desired objective and is not partially dissipated in a circuitous circulation which itself may not be functioning properly.

Charlier (19) showed that deep aerosols on healthy human beings act locally on the bronchopulmonary tree because of the administration of small doses would have a greater effect by this route than by other routes.

these small doses apparently did not result in an intra-arterial re-absorption of the drug into the lungs. Segal (3) demonstrated that Aludrine by inhalation caused minimal side reactions which disappeared quickly in the normal subjects. Subcutaneous injections in the normals lead to marked palpitations, pounding, fullness in the chest, and moderate headache. This seemed to indicate that the toxic effects were due to high blood concentrations. The slight toxicity produced by the inhalation technique indicated the slow reabsorption of the drug into the bloodstream.

According to Charlier (19) when various bronchopulmonary drugs are used by the inhalation method there appears a decrease in hourly pulmonary ventilation, an intensive slowing of the respiratory rate, an important increase of the volume of each respiration, and an increase of carbon dioxide percentage in expired air together with a fall of the alveolar carbon dioxide percent. This results in a decrease in the dead space of the lungs and consequently a rise in the effective ventilation. The changes as stated above after a few inhalations of aerosols of Aludrine cannot be ascribed to any dilatation of the large bronchi but must be induced by both an increase in the size of the smallest bronchioles and also an opening of some pulmonary areas which were not normally working. The coefficient of utilization of inspired air (i.e., effective ventilation divided by total ventilation) which measured normally is about 60% goes up to 90% or more.

Charlier (19) published the results of his five-year study of the treatment of 197 patients suffering from either acute or chronic asthma.

His apparatus consisted mainly of an atomizer and an oxygen tank. The solution from the atomizer was sucked into the oxygen stream so that it could be sprayed as a fine suspension. A device was figured out that would take out the large particles so as to let only the small particles or aerosols get through. This produced a dense mist, extremely thin and absolutely dry. A solution of 0.2% Aludrine was used. Solutions above this concentration were found to produce unpleasant or dangerous side effects due to reabsorption in high degree into the circulation. A technique was developed that would allow aerosols not only to enter deeply into the lungs but also to settle in great amounts on the walls of the smallest bronchioles. These conditions were accomplished when patient was asked to breath slowly and to hold his breath in inspiration for a few seconds, after which he expires deeply. Generally three series of ten consecutive respiratory movements were carried out. All patients were classified according to age and sex, type of dyspnea (paroxysm to chronic) severity of attacks (slight to severe), dominant etiology (bronchitis, hepatic, etc.) and frequency of pathological features (tuberculosis antecedents, etc.). Since the results or degree of improvement varied, the patients were divided into four categories as follows:

1. Where dyspnea occurs almost exclusively as paroxysmal attacks
2. Paroxysmal attacks of severity to occur regularly
3. Patient affected with both chronic and from time to time acute dyspnea
4. Subjects suffering chiefly from chronic dyspnea.

The treated patients were placed in categories as follows:

1. Cases displaying striking improvement, more than 90%. There was a lasting disappearance of asthma (period of at least one year but more often three or four years) whether of paroxysmal attacks in patients who previously suffered from such paroxysms frequently, or of chronic dyspnea and minor asthmatic attacks which used to occur with surprising easiness on various oacasions. This category comprised 10%.

2. Cases greatly improved, approximately 75%. They are relieved of chronic or acute dyspnea but have some breathlessness which is far less disturbing than before and is easily overcome by minor sedative measures. This category comprised 47%.

3. Patients which claim 50% relief of symptoms. Here the acute attacks are far less improvement in frequency, severity and duration, or the chronic dyspnea is much lessened but not entirely removed. This category comprised 25%.

4. Moderate improvement of about 25%. The functional relaxation is often important but it occurs after a large number of sittings only and is generally insufficient anyway. In these patients chiefly the night dyspnea is lessened. This category comprised 6.5%.

5. No improvement. This category comprised 10%.

6. Aggravation in spite of treatment. This category comprised 1.5%.

From this it is shown that 88.5% of patients have improved (first four categories) and 11.5% (categories five and six) have not.

Even patients with severe cases were free of asthma for two to five years after treatment. When dyspnea again occured after a complete

therapeutic course, the severity of the distress was far less because, it was assumed, some pneumodilation remained together with improvement of respiratory dynamics. When dyspnea reappeared, a new pneumodilator "cure" was quite useful and acted as successfully as the first one. It was interesting to note that there was an improvement of the patient's general status as well.

Segal (3) showed that in 86 hospitalized asthmatics treated by Aludrine oxygen-aerosolation there was no increase in systolic pressure and an average increase in pulse pressure of 6 mm Hg. In a study of five normal individuals given Aludrine oxygen-aerosolation there was an average systolic rise of 13 mm Hg with a pulse pressure increase of 16 mm Hg. It is interesting to compare this last study of normal patients given Aludrine to Blumgart's study of the effect of 0.5 to 1.0 cc of 1:1,000 epinephrine given subcutaneously. Here, the average increase in systole was 38 (compared to 13) and an increase of 48 for the pulse pressure (compared to 16). In both studies the increase in pulse rate was essentially the same.

In the study of hospitalized asthmatic patients the lowering of pulse pressure was due almost entirely to a lowering of the diastolic phase due to the peripheral vasodilatation of the finer arterioles.

Gay (10) studied the effects of the inhalation of Aludrine solution on 48 asthmatic patients. An isotonic solution of 1:200 was administered by hand nebulizers. Patients were instructed to take five inhalations at the onset of wheezing and repeat in five minutes if necessary and if no untoward effects appeared. After several trials each patient was able

to determine for himself the optimum number of inhalations and courses to use in his individual case. Of the four routes of administration (sublingual, oral, subcutaneous, and inhalation) the author believed the the inhalation of a nebulized spray produced the most beneficial therapeutic response and the lowest incidence of untoward side actions, All the patients with mild asthma obtained immediate and complete relief after three to six inhalations. Sixteen out of 19 patients with moderate asthma received moderate to marked relief with two to three courses of four to six inhalations. The remaining patients (3) obtained only mild relief. None of the 19 patients failed to obtain some benefit. Sixteen of 21 patients experiencing frequent recurrent paroxysms of severe asthma obtained moderate to marked relief employing one to three courses of six to eight inhalations each.

Most of the cases of severe asthma were those treated in the emergency room or outpatient department because of failure to respond to the usual procedures and medications at home. Responses were quick in every case, beginning in two to three minutes, and reaching its maximum in about five minutes. The optimum dosage in the majority of such cases was about six inhalations. The benefit obtained did not appear to be appreciably increased if more than six inhalations were given in any one course. It was noted consistently that the duration of the relief produced was inversely proportioned to the severity of the asthma, the benefit in extreme cases lasting only about 15 minutes, at which another series of inhalations had to be given. Patients with milder asthma reported relief ranging from

two to twelve hours. Only two patients failed to obtain some benefit from inhalation of Aludrine sulfate mist.

Of these 45 patients, only two experienced palpitation, and questioning revealed that in both instances this occured only after frequent and prolonged use beyond limits set in the instructions. With cessation of the drug, the palpitation in both cases was mild and fleeting.

Gay (10) concluded that Aludrine mist of a 1:200 dilution administered as previously discussed was capable of significant bronchodilating action in mild to severe asthma by way of its local effect on contact within the bronchial tree, and that any amount reaching the systemic circulation was of inadequate concentration to produce subjective toxic effects.

Gay also found that there was a decided increase in expectoration in patients with chronic infective (intrinsic) asthma. Patients reported that their sputum was thinner and more easily raised. This was an early and consistent finding in all such patients treated by this route.

Gay conducted a comparison clinically between Aludrine and epinephrine by inhalations. All patients agreed that Aludrine acted somewhat more rapidly and that the benefit was generally equal to or greater than that produced by epinephrine. Five patients in status asthmaticus and no longer responsive to 1:100 epinephrine inhalation responded to the initial course of Aludrine spray. While the response to Aludrine inhalation was quicker than to epinephrine by inhalation or intramuscular injection, or to aminophylline given intravenously, the duration was definitely shorted than that following the latter drugs.

Lowell (20) in his report of 30 asthmatic patients stated that Aludrine as an aerosol was very effective in relieving mild or moderate severe asthma, but that in severe prolonged attacks, the drug was far less satisfactory. He had 12 patients with severe asthma who received Aludrine. Ten of these, in addition to Aludrine, required intravenous injections of aminophylline, repeated doses of sedatives including demerol, infusions of glucose and saline solution, epinephrine and in some cases oxygen with or without helium. However, patients in whom Aludrine aerosols have become ineffective in removing the more severe attacks of asthma frequently found relief with Aludrine was obtained from milder attacks occurring subsequently.

Dust

Krasmo (21) demonstrated the effectiveness of penicillin dust by negative pressure created by normal breathing during the inspiratory phase. Previously penicillin had been delivered as an aerosol vapor under positive pressure by means of a hand bulb or oxygen tank and guage. The inhalation of penicillin as a dust was shown to have a number of mechanical and therapeutic advantages which included simplicity of equipment and administration, maximum concentration of drug per unit area within the respiratory tract, slow absorption into the systemic circulation, the unnecessary dilution of the drug, the pocket size apparatus which may be kept for instantaneous use at all times, and the lack of necessity of oxygen or a nebulizer required to aerosolize the medicament.

Krasmo (22) showed that the advantages of his method of inhalation

of penicillin dust applied also to Aludrine when used in dust form and therefore widened the application of this new drug.

The use of Aludrine as a dust has paralled the development of a new type of apparatus. This new inhalor or "aerohalor" devised by Abbott and first described by Krasmo consisted of a molded plastic discharge chamber with a detachable mouthpiece. The Aludrine dust is contained in a small plastic cartridge, the bottom of which is fitted with a fine mesh wire screen through which Aludrine dust is released. The upper rim of the cartridge exhibits two small flanges which fit into a groove and allow locking of the cartridge in position in the discharge chamber. The distal end of the discharge chamber is formed into a curved-tube runway containing an aluminum ball. On inhalation the aluminum ball is rapidly drawn up the runway until it strikes the cartridge containing the Aludrine dust; the impact causes a release of a small amount of the Aludrine dust into the discharge chamber. The upper end of the runway is grooved so that the air to be inspired can bypass the aluminum ball after it strikes the cartridge. The inspired air, as it bypasses the ball, carries the release of Aludrine dust into the respiratory passages. Thus with each response a small but uniform amount of dust enters the respiratory passages.

Krasmo (22) investigated the use of Aludrine dust on 24 asthmatic patients. These patients had a history of asthma of 3 to 28 years and were not satisfactorily controlled with the usual drugs. Seven of these patients had an associated bronchitis and 17 had the allergic type of asthma. The patients were instructed to take a whiff of Aludrine dust

during an impending attack and to repeat within one-half to one hour if necessary. He noted that the responses could be classified into two basic groups. Sixteen of the patients were completely and satisfactorily controlled by the exclusive use of Aludrine dust. Eight were controlled by Aludrine only when either aminophylline and iodides and/or antihistamines were used daily. It appeared that the threshhold of bronchospasm lowered by the use of the additional medication made Aludrine more effective in controlling the asthmatic paroxysms. These drugs did not prevent the occurrence of asthmatic attacks but rather made it possible for these paroxysms to yield to norisodrine.

Among these 24 asthmatic patients only four experienced dizziness or palpitation after inhalation. In all cases these symptoms were not alarming and disappeared in ten minutes. On patient consumed as much as 100 mg of Aludrine daily without any untoward reactions whatsoever. Of the 20 patients who had no reactions no tendency of fastness toward the drug was noted after 10 months of use. Krasmo (23) concluded that Aludrine in the form of a dust has a definite place in the symptomatic treatment of asthmatic disease; that it can be inhaled in dust form with a wide margin of safety.

Krasmo (23) in speculating of the fact that Aludrine in 100% concentration does not produce greater side effects conceived that since the drug is in a solid form it remains in the tissues locally for a long time before complete absorption takes place. Yet a certain amount must be absorbed readily since the clinical response occurs within a few minutes.

Swartz (24) concluded that the choice method of administration of

Aludrine was dust inhalation of a 25% amount for the ambulatory severe asthmatic. He thought it less cumbersome than to hand nebulization or self injection; its effect more rapid than the tablet; and that the small plastic inhaler is easily carried on the person and with a little adeptness can be used in public unnoticed. He emphasized that the dosage of Aludrine dust is an individual matter and is determined with each patient specifically. During the course of symptoms, the patient is instructed to take two or three shallow inhalations. Careful watch is kept for time of onset of relief and completeness of relief. If necessary an adjustment is made in the number of inhalations. Once this test dose is determined, the patient is instructed to use this dosage and no more at the earliest sign of symptoms. It is important to emphasize shallow inhalations. Deep inhalations may lead to overdosage and side effects of severity.

Contrary to what Gay and Lowell had demonstrated, Swartz demonstrated that Aludrine in dust form was most effective on severe asthmatics. In his 12 cases of severe asthma, there were 9 excellent, two good, and 1 fair response to Aludrine dust. In his 4 cases of mild asthma, 3 responded unsatisfactorily although 1 had an excellent response. He thought that these results could be explained as follows: Bronchospasm is more apt to play a major role in the asthmatic attack when the condition is of long standing or great severity. This fact plus the experimental evidence of the bronchodilating effect of the drug indicates the efficacy of the drug is based primarily on its effect of bronchodilation. In the early or mild asthmatic, edema of the mucosa is more apt to be the underlying mechanism

of dyspnea and therefore Aludrine would be expected to be less effective.

Kaufman (25) in his study of 63 patients with asthma treated with 25% Aludrine dust by aerohalor, showed that over 60% of these patients derived great benefit. There were 39 excellent results, 13 good to fair, and 12 poor. Side effects were all mild and transitory. In the large majority of cases there was no diminution in therapeudic effects with continued use. The results as indicated here were similar to results of Krasmo and Swartz.

V Side Effects

The presence and degree of side effects of Aludrine is dependent besides the dosage also on the route of administration as indicated previously in the discussion of various routes of administration.

Gay listed the percentage of side effects dependent on the route of administration:

Method and dose	% of side effects
Oral 25-50 mg	80
Oral 15 mg	75
Sublingual 10 mg	33
Subcutaneous 1:1,000	100
Subcutaneous 1:5,000	41
Inhalation 1:200	4

It is obviously seen that inhalation produced by far the smallest percentage of side effects.

Gay also listed the types of side effects most frequently encountered:

Side effect	% of all side effects
1. Palpitation	90
2. Nausea	19
3. Headache	17
4. Nervousness	16
5. Tremor	14
6. Dizziness	13
7. Precordial ache	9
8. Weakness	7
9. Sweating	7
10. Anginal pain	3
11. Epigastric pain	3
12. Vomiting	3
13. Tinnitus	3
14. Flushing of face	1
15. Diarrhea	1

It is noteworthy that palpitation is between four and five times as common as the next most common symptom. Gay (10) studied palpitation and tachycardia in 15 of his patients receiving 0.1 to 0.5 cc of a 1:1,000 dilution of Aludrine. Fourteen experienced a heart rate of 100 beats per minute or above within three to five minutes. The range was 108 to 176 beats per minute. The amount of acceleration corresponded to dosage directly. When 0.1 to 0.2 cc was given the rate returned to preinjection levels within fifteen minutes. When 0.3 to 0.5 was given, the rate persisted for 30 to 60 minutes. The increase in rate began 90 to 120 seconds after injection. These patients experienced palpitation along with the tachycardia.

Although the severity and duration of these symptoms were generally in direct proportion to the size of the dose given, there were a few patients exhibiting unusual sensitivity to the drug, and in these the side effects were always alarming with minimal effective doses. In general the side effects did not tend to decrease in severity or incidence on repeated use of the drug, on the same person.

Gay (10) reported several incidences of side effects of serious import. In three cases acute episodes of typical coronary insufficiency pain were observed (two after taking Aludrine orally and one after a subcutaneous injection of 0.1 cc of 1:1,000. Nine patients showed precordial ache or "heart soreness" in each instance accompanied by palpitation of moderate to marked severity and duration (five following oral doses of 25 mg or greater, three following 10 mg sublingually, one by frequent and prolonged inhalation of 1:200 nebulized mist). All nine patients were

in the 40 to 60 age group. One patient experienced sudden shock (this occurred in a 19 year old boy with status asthmaticus who was epinephrine and aminophylline-fast). He showed a drop in blood pressure from 130/80 to 80/x following the injection of 0.2 cc of 1:1,000 Aludrine. Two other patients experienced precipitous falls in both systolic and diastolic levels three minutes after injection.

Lowell (20) stated that only two of his 30 asthmatic patients had symptoms that might reasonably be attributed to inhalation of Aludrine. In each case nervousness, tachycardia and palpitation were experienced lasting only a few minutes (he indicated that in both cases this was due to overdosage). This agrees approximately with the results of Gay in regard to the percentage of side effects from Aludrine inhalation.

Krasmo showed that of his 24 asthmatic patients receiving Aludrine in the dust form, four experienced dizziness and/or palpitation after inhalation. This was not alarming and disappeared in ten minutes.

Results as to the number and degree of side effects is difficult to evaluate. Epinephrine and aminophylline have a high percentage of "sympathetic" side effects as is generally known. That Aludrine has minimal and fleeting side effects was demonstrated. This was particularly true when the inhalation method of administration was used as compared to other routes The few cases of serious side effects are difficult to evaluate. The pain of coronary insufficiency as mentioned by Gay was not due to coronary constriction since it has been demonstrated that coronary dilation occurs with Aludrine. The plausible explanation is that the contractile stimulating effect on the heart causes a relative insufficiency because of the

increased demands on the myocardium plus an association with a decreased oxygen saturation of the arterial blood due to increased pulmonary resistance, and decreased gaseous exchange. It seems reasonable that this complaint would more apt to present itself in patients with asthma of long duration and consequently demonstrating emphysematous changes. Even though Aludrine may cause bronchodilatation the respiratory exchange would not be greatly increased and the oxygen saturation of the blood would remain about the same. It is conceivable under such circumstances that the myocardial stimulating effects of the drug may cause some degree of coronary insufficiency.

The other serious side effect, circulatory collapse, is plausible on the basis of the vasodilating effect of the drug. That certain individuals may be more subject to vasomotor changes than others is not difficult to imagine.

Sheldon (1951) noted that Aludrine, like epinephrine, appears to influence the degree of whealing response of the skin, particularly to the intracutaneous test. Therefore, the allergist performing skin tests especially during intradermal technique, should withhold Aludrine for several hours before and after skin testing procedures since this drug may alter the skin test result.

Tolerance

Charlier (19) stated as previously discussed that his patients with severe asthma had been free from asthma for two to five years following treatment. When dyspnea again occured after a complete therapeutic course,

the severity of the distress was far less. When dyspnea reappeared a new "pneumodilator cure" was quite useful and acted as successfully as the first one.

Herxheimer (16) stated, however, that tolerance is acquired by some patients. Two of his patients in moderate status asthmaticus with a constant reduced vital capacity had an increase in their vitalcapacities after their daily doses of Aludrine during the first two days. On the third day the increase was slightly less and on the fourth day it was so small that it lay within the margin of experimental error. A third patient had severe attacks two or three times in 24 hours which could be checked with adrenaline or with Aludrine. On 0.04 gm three times per day he remained free for 36 hours; then an attack developed which was not completely checked with 0.4 gm of Aludrine. On the third day another attack developed and the experiment was then stopped.

Kaufman (25) stated that in the majority of his cases that improved under Aludrine treatment there was no diminution in the therapeutic effect with the continued use of the drug. However, then he notes that in a few patients who at first had excellent or good results, reported some diminution in the beneficial effect with continued use.

VI Other clinical uses of Aludrine

Nathanson (8) demonstrated that Aludrine could restore the cardiac rhythm in patients where cardiac standstill had been induced by carotid sinus pressure. This suggests the possible use of this drug in patients having the carotid sinus syndrome.

Nathanson (8) demonstrated the return of normal cardiac rhythm in patients with cardiac standstill. In all cases there was an increase in the rate of ventricular rate when Aludrine was given. It was suggested that this drug be used in the therapy of sudden cessation of cardiac activity (as during surgical procedures). It may be more valuable than epinephrine because Aludrine apparently does not predispose to ventricular fibrillation (Garb (9)).

Other effects of Aludrine have been mentioned in the literature from time to time. Swartz (24) noted in one patient suffering menopausal symptoms as well as asthma, Aludrine aborted the "flush" attack and seemed to prevent attacks that arose after the injection of hormone. He also noted in one patient whose asthma was complicated by bouts of abdominal pain, eructation and nausea, Aludrine also relieved the gastrointestinal symptoms. These also occurred independent of the asthmatic paroxysms but had disappeared almost entirely during the period of Aludrine usage. These cases are difficult to evaluate. The effective use of Aludrine for menopausal symptoms and gastrointestinal disturbances certainly would seem dubious.

Effects other than bronchodilation have been reported. Charlier(19)

stated that the general status of the asthmatic was improved. In his five-year study of 197 patients he noted that there was a great increase in appetite, a digestive tolerance for "asthmatogic" food, an increase in weight up to 12 or 15% (even in the case of apatient previously in satisfactory general state), an increase in effort capacity, and a general feeling of well being. He showed, as others did later, that sputum almost immediately became thinner and expectoration quite easy; this expectorant power of aerosols is important and lasting and much greater than that of the usual expectorant drugs. He observed that with several inhalation sittings expectoration is gradually reduced and clearing of sibilant rales takes place. Finally, the patients became quite free.

Lowell (20) studied the effects of Aludrine in the prevention of asthma-like attacks. Subjects were given 0.02 mg of histamine. This was followed by a drop of approximately 1,000 cc in vital capacity. This is the type of response which occurs in the great majority of asthmatic patients. After 20 minutes the vital capacity was back to normal. Aludrine 0.1 mg intramuscularly was then given causing a bounding pulse and an increase of pulse rate of 40 beats per minute. There was marked nervousness, palpitation and faintness experienced, but these symptoms disappeared in ten minutes. The vital capacity had increased approximately 100 cc above normal. This was followed by another 0.02 mg of histamine. No changes either subjectively or objectively were noted. There was no change in the vital capacity. The other systemic effects of histamine

(e.g. gaseous taste in mouth, flushing and headache) were not prevented by Aludrine. It was apparent from this that Aludrine blocked the action of histamine in a manner similar to epinephrine.

Methacholine was then used in a manner similar to that above and the results were approximately the same. The blocking action of methacholine was lost within 30 minutes of the administration of Aludrine. Lowell concluded that Aludrine furnishes potent protection against the reduction in vital capacity and asthma-like attacks induced by the parenteral administration of histamine and methacholine.

The use of Aludrine with other drugs

Krasmo (22) noted that 8 of his asthmatic patients were controlled by Aludrine only when either aminophylline and iodides and/or antihistaminics were used daily. It appeared that the threshold of bronchospasm lowered by the use of the additional medication made Aludrine more effective in controlling the asthmatic paroxysms. These drugs did not prevent the occurence of asthmatic attacks but rather made it possible for these paroxysms to yield to norisodrine.

Dautrebande (28) demonstrated that Aludrine and adreanol can usefully be combined for aerosol therapy of asthma and bronchitis. These two drugs act synergistically. The same synergistic effect can be observed after oral administration of the drugs in relatively small doses.

Charlier (29) noted that the antidyspnoeic action of Aludrine aerosols is potentiated and prolonged by polyvinylpyrrolidone (solution 12.5%). This was not due to viscosity changes. Polyvinylpyrrolidone alone has no effect. Whether this will have any clinical use remains to be seen.

VII Summary

Aludrine, the isopropyl derivative of epinephrine, was first described by Konzett in 1940. It was found that the drug had a bronchodilating action approximately ten times that of epinephrine. Early studies showed an extremely low toxicity. Aludrine was superior to all derivatives of epinephrine tested and was surpassed by only two in low toxicity (these two compounds had only slightly lower toxicity but had a very much less bronchodilating effect than Aludrine).

Although Aludrine had a bronchodilating effect like epinephrine, its other pharmacological properties are quite different. It has been shown by numerous investigators that Aludrine causes a drop in blood pressure rather than an elevation, as is the case with epinephrine. This seems to be true also of the pulmonary circulation. The mechanism involved seems to be vasodilation. Aludrine stimulates myocardial contractability, thereby increasing heart rate; causes moderate dilation of the coronary vessels, and increases the force of contraction. Aludrine has a definite effect on the rhythmic properties of the heart; it restores activity of the sinus node or initiates ectopic pacemakers following cardiac standstill; however, it does not predispose to auricular fibrillation as does epinephrine. A characteristic electrocardiogram is produced in man following Aludrine administration. This includes a depression of the S-T junction and a trough-like configuration suggesting augmentation of the auricular T waves.

Soon after the bronchodilating effects of the drug was demonstrated,

studies were conducted to investigate the possibilities of Aludrine for the symptomatic treatment of bronchial asthma. Although most of these studies depended on subjective data obtained from the patient, objective information was obtained by measuring the vital capacity before and after treatment, the use of placebos, and the evaluation of treatment carried out over relatively long periods of time. Many different routes of administration were attempted. These included oral, subcutaneous, sublingual, and inhalation. It was shown quite early that the inhalation method seemed to provide the greatest relief of bronchospasm with the least undesirable side effects for the patient. Following the effective use of penicillin by inhalation of the dust form, inhalation of Aludrine dust was investigated. The therapeudic results were as good and if not better than the use of the nebulized spray, and eliminated the need for a bulky piece of apparatus. Aludrine dust could be inhaled from a small inhalor which could be carried on the person for immediate use. Since it was shown that the dosage varied widely according to the individual patient, this apparatus also provided a good method for the gradation of individual dosages.

All investigators studying the clinical effects of Aludrine have shown that Aludrine has effectively reduced bronchospasm in the great majority of patients treated. It was generally agreed that the earlier the treatment was begun, the more effective it would be. There was some disagreement as to the degree of severity of the asthmatic attack which would best respond to the drug. Most investigators have demonstrated that

the mild cases respond best and that the effectiveness of symptomatic relief varies inversely to the severity of the attack. It is noteworthy that Aludrine has given relief when epinephrine no longer has had any effect.

There have been a number of side effects reported following the use of the drug. These have usually been associated with the sympathomimetic effect of the drug: palpitation (tachycardia) comprised 90% of all side effects. A few incidences of more serious side effects were reported. These included attacks mimicing angina pectoris and shock. The angina was probably due to coronary insufficiency created by increased heart action superimposed on an anoxemia associated with impared respiratory exchange.

Too few studies have been carried out to evaluate the drug in regard to tolerance with continued use. Most reports show that the large majority of patients can use Aludrine for long periods of time (up to five years) without the development of resistance. There have been a few cases of tolerance developing in a matter of days; some patients also develop a diminution in the beneficial effect after continued use (months). It also has been shown that where a complete therapeutic course has been given and the treatment was discontinued, that with the reappearance of dyspnea, the subsequent use of Aludrine was as effective as the original treatment.

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VIII Conclusion

It seems that Aludrine particularly in the form of the dust has a definite place in the symptomatic treatment of bronchial asthma, and provides a new approach to the abolition of the oncoming paroxysm.

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