Wood and Hadley [16] reported ninety-five cases during the autumn and winter and only fourteen in the spring and summer. Of 612 attacks in our series (table 3), however, 51.3 per cent occurred between October and April and 48.7 per cent in the spring and summer. The element of cold, therefore, seems to have no rôle in the formation of a coronary thrombus.

Recently, much has been written concerning the important effect of the use of tobacco on cardiovascular disease, including thrombosis. We therefore investigated this point. Table 4 shows that one third of the men and practically all the women were nonsmokers. Furthermore, the proportion of heavy and moderate smokers did not differ from that of society in general. Therefore, we believe that tobacco has no influence on the occurrence of coronary thrombosis. White and Sharber [17] came to a similar conclusion concerning coronary sclerosis.

A glance at table 5 makes it obvious that alcohol also has no rôle in coronary thrombosis, since more than half the patients did not drink at all. In fact, it may protect, since only 4 per cent of our patients were heavy drinkers. It is noteworthy that in only one case did occlusion follow a drinking bout.

COMMENT

From the foregoing report it would seem that the onset of coronary artery thrombosis during the various states considered was merely a temporal coincidence and that no specific factor precipitates an attack. This contrasts with the situation in angina pectoris, which is often confused with coronary thrombosis. While both conditions are probably manifestations of a metabolic disturbance, as Libman [18] stated, and while the local pathologic process is sclerosis of the coronary artery, yet the two conditions differ widely. Angina pectoris is a functional syndrome. It appears when there is temporary insufficiency of coronary blood flow as a result of exertion or reflex spasm. The nervous element is paramount. Although some attacks of angina pectoris occur without discernible cause, the majority are definitely related to specific acts, such as playing golf, walking against the wind, eating a meal or excitement. The attack is relieved by glyceryl trinitrate. Coronary thrombosis, on the contrary, occurs irrespective of rest, activity, excitement or emotion and season or temperature and is not helped by glyceryl trinitrate. It is not our intention to minimize the value of physical and mental rest in the treatment of chronic disease of the coronary artery, but thus far medicine has been unable to prevent the formation of a thrombus.

SUMMARY

A statistical study of over 800 attacks of coronary thrombosis was made to determine what factors may have initiated the thrombosis.

Coronary thrombosis occurred in all walks of life and in all types of occupations.

Although 40 per cent of the attacks occurred during rest or sleep, this was probably a coincidence, since half the day is ordinarily spent in these states.

Exertion, even severe, was of little or no significance in the precipitation of an attack. This held good for walking, straining at stool, coitus and playing golf.

Excitement, ingestion of food, infection, tobacco, alcohol, heart failure, time of day and season of year were found to have no significance.

The effect of operation and of insulin require further study.

Although both angina pectoris and coronary artery thrombosis have the same underlying pathologic condition, namely, coronary sclerosis, they differ entirely in respect to the exciting cause of the attack.

125 East Seventy-Second Street.

17. White, P. D., and Sharber, Trimble: Tobacco, Alcohol and Angina Pectoris, J. A. M. A. **102**: 655 (March 3) 1934.

18. Libman, Emanuel: Symposium: Angina Pectoris, with Special Reference to Coronary Artery Disease, Bull. New York Acad. Med. **11**: 427 (July) 1935.

CLINICAL OBSERVATIONS ON THE EFFECT OF BENZEDRINE SULFATE

A STUDY OF PATIENTS WITH STATES OF CHRONIC EXHAUSTION, DEPRESSION AND PSYCHONEUROSIS

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Pharmacologic studies [1] of benzedrine (beta-aminopropylbenzene or benzyl methyl carbinamine) indicate that it has a sympathomimetic action and a profound stimulating effect on the central nervous system. Clinically its sympathomimetic action has been utilized particularly in the treatment of congestion of the nasal mucosa,[2] in maintaining blood pressure during spinal

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1. Pharmacologic studies:

Barger, G., and Dale, H. H.: Chemical Structure and Sympathomimetic Action of Amines, J. Physiol. **41**: 19-59 (Oct. 11) 1910.

Piness, George; Miller, Hyman, and Alles, G. A.: Clinical Observations on Phenylaminoethanol Sulfate, J. A. M. A. **94**: 790-791 (March 15) 1930.

Hartung, W. H., and Munch, J. C.: Amino Alcohols: VI. The Preparation and Pharmacodynamic Activity of Four Isomeric Phenylpropylamines, J. Am. Chem. Soc. **53**: 1875-1879 (May) 1931.

Alles, G. A.: The Comparative Physiological Action of dl-Beta-Phenylisopropylamine: I. Pressor Effect and Toxicity, J. Pharmacol. & Exper. Therap. **47**: 339-354 (March) 1933.

Tainter, M. L.: Comparative Actions of Sympathomimetic Compounds: Phenyl and Substituted Phenyl Derivatives, Nonphenylic Ring Compounds and Aliphatic Amines, Arch. internat. de pharmacodyn. et de thérap. **46**: 192-232 (Oct. 15) 1933.

Alles, G. A., and Prinzmetal, Myron: The Comparative Physiological Actions of the dl-Beta-Phenylisopropylamines: II. Bronchial Effect, J. Pharmacol. & Exper. Therap. **48**: 161-174 (June) 1933.

Myerson, Abraham; Loman, Julius, and Dameshek, William: Physiologic Effects of Benzedrine and Its Relationship to Other Drugs Affecting the Autonomic Nervous System, Am. J. M. Sc. **192**: 560-574 (Oct.) 1936.

Lagen, J. B.; Soley, M. H., and Leake, T. B.: Effect of Benzedrine Sulfate on Basal Metabolic Rate, Proc. Soc. Exper. Biol. & Med. **35**: 276-278 (Nov.) 1936.

Myerson, Abraham; Rinkel, Max, and Dameshek, William: The Autonomic Pharmacology of the Gastric Juices, New England J. Med. **215**: 1005-1013 (Nov. 26) 1936.

Schube, P. G.; Ritvo, Max; Myerson, Abraham, and Lambert, Ruth: Human Autonomic Pharmacology: IV. The Effect of Benzedrine Sulfate on the Gallbladder, ibid. **216**: 694-697 (April 22) 1937.

2. Clinical studies:

Giordana, A. A. S.: Benzyl Methyl Carbinamine (Benzedrine): A Study of the Rapidity and Duration of Its Shrinking Action in the Nasal Turbinates, Pennsylvania M. J. **39**: 20-22 (Oct.) 1935.

Hulka, J. H.: A Simple Method of Introducing Benzedrine Vapors into Eustachian Tube, Arch. Otolaryng. **23**: 692-693 (June) 1936.

Wood, E. L.: Use of Benzedrine in Eustachian Tube and Middle Ear with Apparatus for Application, J. M. Soc. New Jersey **33**: 410 (July) 1936.

Sulman, L. D.: Certain Conditions in Which Volatile Vasoconstrictor Has Proved of Particular Value: Preliminary Report, M. Times & Long Island M. J. **63**: 374-375 (Dec.) 1935.

Bertolet, T. A.: Benzyl Methyl Carbinamine Carbonate: A Report Based on Its Clinical Effect in One Hundred and Twenty-Two Rhinological Cases, M. J. & Rec. **136**: 75-76 (July 20) 1932.

Byrne, H. V.: The Use of Benzyl-Methyl-Carbinamine-Carbonate in the Treatment of Rhinitis, New England J. Med. **209**: 1048-1051 (Nov. 23) 1933.

Scarano, J. A.: Rapidity of Shrinkage and Immediate and Secondary Reactions Following Applications of Ephedrine and Benzedrine, M. Rec. **140**: 602-604 (Dec. 5) 1934.

Wood, E. L.: A New Drug for Treatment of the Eustachian Tube and Middle Ear, with an Apparatus for Its Use, Arch. Otolaryng. **21**: 588-590 (May) 1935.

anesthesia [3] and in orthostatic hypotension,[4] and for the relief of spasm affecting the gastro-intestinal tract.[5] The stimulating effect on the central nervous system has led to observations on the effect of benzedrine in many psychiatric and neurologic conditions, including narcolepsy,[6] disorders of mood and affect (chiefly depression [7]), postencephalitic parkinsonism,[8] psychoneurosis,[9] and to observations on its effect on normal persons and on those [10] suffering from states of exhaustion.[11]

The method by which benzedrine produces a stimulating action on the central nervous system and the part of the brain which it stimulates is unknown. Marked stimulation of the nervous system is the most striking effect of the drug. The long duration of this effect is noteworthy. From the evidence which has so far accumulated, benzedrine does not appear to be toxic in usual doses nor does it seem to be habit forming.

This report, which supplements a previous one,[12] is concerned with the effects of administration of the drug to 100 patients during a short time and to forty-four patients during periods varying from two weeks to eight months. All of these patients were carefully examined and had no detectable evidence of organic disease. The drug was administered orally, in the form of the sulfate, in doses of from 2.5 to 20 mg. before breakfast and frequently the dose was repeated at noon. In all our work the sulfate was used. A placebo tablet, identical in appearance with that which contained benzedrine, was administered on occasions and failed regularly to cause any change of symptoms.

We have divided the 100 cases, according to the symptoms, in three groups under the headings (1) chronic exhaustion, (2) psychoneurosis and (3) depression. To distinguish clearly between a state of chronic exhaustion and a psychoneurosis often is difficult if not impossible. For the purposes of this presentation, states of chronic exhaustion may be considered to be characterized by persistent sensations of fatigue, lack of energy and lassitude, for which no organic cause can be determined. These sensations may be part of a syndrome of biologic inferiority or may result from environmental difficulties, overwork or infections. A description of many of the features of this syndrome, and justification for the diagnosis, have been given previously by Macy and Allen.[13] The term "psychoneurosis" is used in this presentation to designate the condition of a group of patients whose chief symptoms were nervousness, anxiety, restlessness, irritability, inability to relax and who had numerous somatic symptoms. In this group of cases fatigue ordinarily was not a prominent symptom. It is frequently difficult to evaluate the results of any form of treatment if patients are subject to nervous and mental disorders and fatigue states, because of the marked variability in the course of these conditions. We cannot say definitely that the use of benzedrine was responsible for all the beneficial effects noted in our study, for reassurance of the absence of organic disease, correction of environmental difficulties, and rearrangement of methods of living, as well as other factors, may have contributed significantly to improvement.

CHRONIC EXHAUSTION

Immediate Effects.—The effects of one or two doses of benzedrine on thirty-two patients who had chronic exhaustion are noted in table 1. The condition of twenty-five, or 78 per cent, of the patients was improved following the use of benzedrine. In some instances the results were spectacular, leading to complete disappearance of exhaustion, marked exhilaration and increased capacity for physical and mental work. Along with this there were, in some cases extraversion of thought and activity, speeding of mental processes, cheerfulness, elation and loquaciousness. Vague neuromuscular aches and pains and consciousness of abdominal discomfort frequently were greatly benefited or entirely relieved. When symptoms such as nervousness, anxiety, restlessness and irritability were present, they were frequently uninfluenced or even accentuated. Many of these patients stated that they felt "jittery" or stimulated and that they noted dryness of the mouth, palpitation, tremor and excessive sweating. Some of these unpleasant symptoms which frequently followed the use of the drug and outweighed its beneficial effects may have been the result of the administration of the rather large amounts of the drug that were required to relieve fatigue.

Effects of Prolonged Administration.—The effects of benzedrine administered daily for from two weeks to eight months, in doses of from 2.5 to 20 mg. once or twice daily, were studied in twenty-three cases of chronic exhaustion in which the immediate effects of the drug were beneficial. The results are indicated in table 2. Improvement of the condition of seven patients (30 per cent) continued for from three weeks to four months while they used the drug, but they discontinued the use of it after variable periods because improvement was only slight, because of the subsequent development of undesirable effects or because the

3. Tovell, R. M.: Control of Blood Pressure During Spinal Anesthesia: Preliminary Report of the Use of Benzedrine, Proc. Staff Meet., Mayo Clin. **11**: 585-588 (Sept. 9) 1936.

4. Davis, P. L., and Shumway-Davis, Margaret: Orthostatic Hypotension: The Treatment of Two Cases with Benzedrine Sulfate, J. A. M. A. **108**: 1247-1249 (April 10) 1937. Korns, H. M., and Randall, W. L.: Orthostatic Hypotension Treated with Benzedrine: Report of Case, Am. Heart J. **13**: 114-118 (Jan.) 1937.

5. Myerson, Abraham, and Ritvo, Max: Benzedrine Sulfate and Its Value in Spasm of the Gastro-Intestinal Tract, J. A. M. A. **107**: 24-26 (July 4) 1936. Ritvo, Max: Drugs as an Aid in Roentgen Examination of the Gastro-Intestinal Tract: The Use of Mecholyl, Physostigmine and Benzedrine in Overcoming Atonicity, Sluggishness of Peristalsis, and Spasm, Am. J. Roentgenol. **36**: 868-874 (Dec.) 1936.

6. Effect in narcolepsy:
Prinzmetal, Myron, and Bloomberg, Wilfred: The Use of Benzedrine for the Treatment of Narcolepsy, J. A. M. A. **105**: 2051-2054 (Dec. 21) 1935.
Ulrich, Helmuth; Trapp, C. E., and Vigdoff, Ben: The Treatment of Narcolepsy with Benzedrine Sulfate, Ann. Int. Med. **9**: 1213-1221 (March) 1936.
Nathanson, M. H.: The Central Action of Beta-Aminopropylbenzene (Benzedrine), J. A. M. A. **108**: 528-531 (Feb. 13) 1937.
Guttman, Erich, and Sargant, William: Observations on Benzedrine, Brit. M. J. **1**: 1013-1015 (May 15) 1937.

7. Effect in disorders of mood and affect:
Schube, P. G.; McManamy, M. C., and Trapp, C. E.: Unpublished Data.
Myerson, Abraham: Effect of Benzedrine Sulfate on Mood and Fatigue in Normal and Neurotic Persons, Arch. Neurol. & Psychiat. **36**: 816-822 (Oct.) 1936.
Davidoff, Eugene: A Clinical Study of the Effect of Benzedrine Therapy on Self-Absorbed Patients, Psychiat. Quart. **10**: 652-659 (Oct.) 1936.
Guttmann, Erich: Effect of Benzedrine on Depressive States, J. Ment. Sc. **82**: 618-620 (Sept.) 1936.
Nathanson.[6]
Guttmann and Sargant.[6]
Wilbur, MacLean and Allen.[12]
Davidoff and Reifenstein.[14]
Sargant and Blackburn.[15]

8. (*a*) Solomon, Philip; Mitchell, R. S., and Prinzmetal, Myron: The Use of Benzedrine Sulfate in Postencephalitic Parkinson's Disease, J. A. M. A. **108**: 1765-1770 (May 22) 1937. (*b*) Solomon, Philip, and Prinzmetal, Myron: The Use of Benzedrine in Postencephalitic Parkinsonism, J. Nerv. & Ment. Dis. **85**: 202 (Feb.) 1937.

9. Myerson, Abraham: The Physiological and Psychological Effects of Benzedrine, ibid. **85**: 202-206 (Feb.) 1937. Myerson.[7] Davidoff.[7] Wilbur, MacLean and Allen.[12]

10. Nathanson.[6] Myerson.[7] Wilbur, MacLean and Allen.[12]. Davidoff and Reifenstein.[14] Myerson.[9]

11. Nathanson.[6] Myerson.[7] Wilbur, MacLean and Allen.[12]

12. Wilbur, D. L.; MacLean, A. R., and Allen, E. V.: Clinical Observations on the Effect of Benzedrine Sulfate, Proc. Staff Meet., Mayo Clin. **12**: 97-104 (Feb. 17) 1937; abstr., J. A. M. A. **108**: 587-588 (Feb. 13) 1937.

13. Macy, J. W., and Allen, E. V.: A Justification of the Diagnosis of Chronic Nervous Exhaustion, Ann. Int. Med. **7**: 861-867 (Jan.) 1934.

effect of the drug eventually wore off entirely. As often expressed by the patient, "the effect wore off" or "I seemed to get used to it." Five patients (22 per cent) felt improved during use of benzedrine over periods of from one week to one month but discontinued the use of it because unpleasant effects noted previously continued and offset the beneficial effects. Eleven patients (48 per cent) are continuing to use benzedrine after periods of from one to eight months and feel that the favorable effects have persisted.

TABLE 1.—*Immediate Effects of Administration of Benzedrine*

Diagnosis	Number of Patients: Worse	No Change	Improved	Total	Percentage of Patients Improved
Psychoneurosis	12	7	16	35	45.7
Depression	5	4	21	30	70.0
Exhaustion	3	4	25	32	78.1
Total	20	15	62	97*	63.9

* Three patients not included in the table had depression associated with chronic alcoholism.

A review of the records of the patients whose condition was improved and of those for whom improvement was only temporary or was associated with unpleasant symptoms failed to reveal any distinguishing features that could be used to explain the divergent results. The following report of a case illustrates the gradual loss of effect that may occur even though the immediate result was remarkable:

CASE 1.—A man, aged 27, came to the clinic complaining of headaches, constipation and marked fatigue of three years' duration. He was so fatigued that he had been unable to complete his studies as a law student. Extensive clinical, roentgenologic and laboratory examinations failed to reveal evidence of organic disease, and a diagnosis of chronic exhaustion was made. The patient was given 20 mg. of benzedrine before breakfast and 20 mg. before lunch, following which he stated that he noticed very marked relief of fatigue and a markedly increased desire and capacity for physical and mental effort. He felt that "a cloud had been lifted from his brain"; he regained his former confidence and "felt normal for the first time in three years." During the day he played twenty-seven holes of golf without particular fatigue, whereas previously nine holes had been thoroughly sufficient to exhaust him. Previously noted muscular aches and vague abdominal discomfort disappeared. The patient was advised to take benzedrine in amounts of 20 mg. before breakfast and 10 mg. before lunch for a trial period. One month later he reported that his condition was so much improved that he seriously contemplated returning to law school. Five months after his examination at the clinic, his condition was still much improved. He had returned to law school and was working continuously with reasonably good success. However, he was taking benzedrine in a dose of 10 mg. every three days because otherwise it lost its effect. Seven months after his first visit to the clinic he reported complete exhaustion at the end of the day and inability to concentrate, which were symptoms of which he originally complained. Benzedrine not only was no longer useful in overcoming these symptoms but it made him "terribly irritable."

The following case is illustrative of persistent improvement following administration of benzedrine for eight months:

CASE 2.—A woman, aged 28, came to the clinic complaining of exhaustion of three years' duration. The feeling of tiredness had begun while she was teaching and had progressed to such an extent that she had been obliged to give up her work. She rapidly lost interest in all activities and for one year she had required from twelve to thirteen hours of sleep daily. Despite the fact that her appetite was large she felt that she did not get "any energy out of her food." Extensive examination failed to reveal evidence of organic disease and a diagnosis of chronic exhaustion was made. The patient was given 20 mg. of benzedrine before breakfast and 10 mg. before lunch, following which she stated that she obtained marked relief from fatigue and that she felt better than she had felt for four years. The improvement was so marked that she did many things, such as cleaning her room, which she had not done for a long time. The patient was advised to take benzedrine in amounts of 20 mg. before breakfast and 10 mg. before lunch for a trial period. At the end of eight months, during which the daily dose of benzedrine had been continued, the patient reported that she still experienced very marked increase of energy, increase of desire and capacity for physical and mental effort, as well as a marked feeling of well being and exhilaration There had been no change in blood pressure, which had been normal when she was originally examined at the clinic. Her appetite had been persistently lessened since taking benzedrine and it had been a little more difficult for her to sleep than it was previous to her taking the drug. However, the patient wrote that she felt "like living."

PSYCHONEUROSIS

Immediate Effects.—The immediate effects of benzedrine on a group of thirty-five patients on whom a diagnosis of psychoneurosis was made are presented in table 1. The dominant symptoms noted were nervousness, anxiety, inability to relax, and lack of energy. If exhaustion was present, frequently it was improved but the dominant symptoms were frequently exaggerated. In many instances it was possible to predict beforehand the results to be obtained with benzedrine in this group of cases. It will be noted that the percentage of psychoneurotic patients who obtained immediate good results was not as large as was the corresponding percentage of patients who had chronic exhaustion and we have noted, in addition, that the degree of improvement of patients with psychoneurosis was less striking. Many of them noted that unpleasant symptoms were accentuated by administration of the drug. Because of the foregoing observations, the effect of prolonged administration of benzedrine on patients with psychoneurosis has not been studied.

DEPRESSION

Immediate Effects.—Of a group of thirty patients who were suffering from depression, the immediate effects of benzedrine were striking on twenty-one, or 70 per cent (table 1). These patients were carefully selected; depression, with mental and physical slowing, was the predominant feature of the clinical picture. Patients who had marked anxiety and physical and mental hyperactivity associated with depression were not ordinarily benefited by benzedrine, for the symptoms mentioned were accentuated. Of twenty patients who had simple or reactive depression, fourteen experienced marked relief, four noted no change and the condition of two became worse. Of ten patients who were in the depressed phase of manic depressive psychosis, seven experienced marked relief and three

TABLE 2.—*Effects of Continued Administration of Benzedrine in Cases of Chronic Exhaustion* *

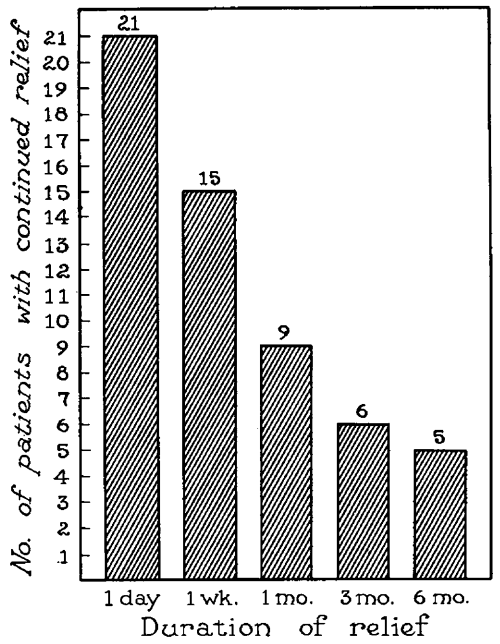
Result	Cases: Number	Per Cent	Duration of Treatment, Weeks
Continued improvement	11	47.8	1-32
Improvement but administration discontinued	7†	30.4	3-12
	5‡	21.8	1- 4
Total	23	100.0	

* The immediate effect of the drug was beneficial in all cases.
† After variable periods because (*a*) improvement was slight, (*b*) effect wore off, (*c*) undesirable effects developed.
‡ Because associated unpleasant symptoms persisted.

noted exacerbation of symptoms. The patients who experienced relief were not severely depressed.

Three patients not included in table 1 who had depression associated with chronic alcoholism were greatly benefited by benzedrine, which appeared to act as a supplementary stimulant.

Effects of Continued Administration.—Although the immediate results of administration of benzedrine to depressed individuals were excellent, our experience with its continued use in this group has been disappointing, as shown in the chart. Twenty-one patients whose initial response to benzedrine was excellent continued to take the drug for variable periods. Thirteen had simple depression and eight had the depression of a manic-depressive psychosis. Of these twenty-one depressed individuals, six reported that in spite of continued medication the initial favorable results were not repeated after the first week. Because benzedrine failed to relieve their condition, an additional six



Decreasing effect of continued administration of benzedrine to patients who are in states of depression.

patients discontinued its use in one month and three more patients discontinued its use at the end of three months. Six remain to be accounted for. Of these, one discontinued use of the drug before six months had elapsed and five reported after six months that they continued to obtain relief from the medicine. It is obvious that relief of depression as a result of administration of benzedrine is temporary in many instances.

The following report of a case is illustrative of the persistent improvement following continued administration of benzedrine:

CASE 3.—A man, aged 45, was seen at the clinic in August 1936. Since 1918 he had suffered from repeated episodes of depression, which had alternated with periods of mild exaltation. When examined at the clinic he had been depressed for a year and was unable to work. Examination of the patient did not reveal significant abnormalities. Twenty milligrams of benzedrine given by mouth resulted in marked relief and the patient was dismissed with instructions to take 10 mg. of benzedrine in the morning and again at noon. Three months later he wrote the following letter:

"As soon as I started taking the benzedrine the depression and feeling of fear left me at once. It felt like the 'do or die' emotion had come to life again and had driven the fear feeling out of my mind; or in other words it made me feel like I have felt before under normal conditions when I have been at my best of vigour. Due to luck I was able to obtain work, and was able to put it over the first week and the firm seemed satisfied, and as time has gone on I have gathered more confidence in myself. I now sleep well without the use of sleeping tablets, and I do not have those terrible regrets in the morning, but I still have a strong tendency to day dream and am too weak yet to withstand any real disappointment."

The following report of a case illustrates gradual loss of effect from continued use of benzedrine, even when effects of the initial administration were excellent:

CASE 4.—A man, aged 52, was examined at the clinic in July 1936 because of mental depression. In 1925 he had suffered from depression for six months following financial reverses. He had recovered completely from this episode but there had been a recurrence in 1927 which had lasted one year. In 1930 he had become depressed again; this state had lasted for two years but he again had recovered completely. The episode of depression at the time of examination had begun in 1935 and had continued with no remission. During the states of depression the man was obsessed with suicidal thoughts and it was only with the greatest difficulty that he could tend to his personal needs. He was unable to work. Following administration of 20 mg. of benzedrine there was a marked change in mood. The patient became happy and confident and there was marked increase in psychic and motor activity. He went to two motion picture shows on the day he took the benzedrine; he said that he was able to follow the action closely and that he had enjoyed himself for the first time in a year. He was dismissed with instructions to take 10 mg. of benzedrine in the morning and again at noon. Two months later he was again examined at the clinic. He complained that although he had continued the daily use of benzedrine, and had been greatly relieved for a month, the drug was failing in its effect. His depression had returned and it was impossible for him to work. The dosage of benzedrine was increased to 30 mg. a day but no benefit resulted. Medication has been continued for six months but the patient never again has experienced the marked relief that was so evident during the first few weeks of administration of benezdrine.

UNFAVORABLE EFFECTS

The unfavorable effects of one or two doses of benzedrine have been noted previously and include exaggeration of nervousness, apprehension and anxiety, a feeling of being "fidgety" or "jittery" and insomnia, excessive sweating, dryness of the mouth, light headedness, irritability and melancholia. Some patients who have continued to take benzedrine for periods of weeks or months occasionally have noted persistence of these symptoms or development of them. We have not noted unfavorable gastro-intestinal symptoms, such as abdominal cramps and an increased desire to go to stool, which other observers [14] have reported.

Loss of weight, apparently resulting from reduced appetite and increased activity, have been noted by some observers [15] as an unfavorable effect of the drug. It has been suggested that the relative anorexia results from diminished tonus of the gastro-intestinal tract. Of the twenty-three patients with chronic exhaustion who took benzedrine from two weeks to eight months, two reported loss of 20 pounds (9 Kg.) after using benzedrine for two and four months respectively. Two patients, however, reported a gain of 5 and 6 pounds (2.3 and 2.7 Kg.) respectively and the weight of the remainder did not change significantly. One possible harmful effect of prolonged administration of benzedrine may be encountered if the drug is given to patients whose exhaustion or fatigue is a protective

14. Davidoff, Eugene, and Reifenstein, E. C.: The Stimulating Action of Benzedrine Sulfate: A Comparative Study of the Responses of Normal Persons and of Depressed Patients, J. A. M. A. **108**: 1770-1776 (May 22) 1937.

15. Nathanson.[6] Davidoff and Reifenstein.[14]

symptom; abolishment of the exhaustion or fatigue may result in expenditure of energy beyond the capacity of the individual.

There are no reports in the literature to suggest that use of benzedrine leads to formation of a habit, and because of its chemical structure one would not anticipate such an effect. The possibility of formation of a habit is not excluded, however. The first patient with narcolepsy to whom Prinzmetal and Bloomberg [6] reported giving the drug is still taking the same dose after three years.

That benzedrine may cause elevation of the blood pressure for periods varying from five to seven hours has been noted by several observers.[16] In at least one case (case 5) when benzedrine was given in relatively small doses to an elderly patient who had hypertension, undesirable increases in blood pressure and cardiac symptoms were produced.

In the following two cases, alarming symptoms referable to the heart arose in the course of treatment with benzedrine:

CASE 5.—A woman, aged 72, who had received treatment for carcinoma of the breast and who had essential hypertension, came to the clinic because of a feeling of depression of several months' duration. She stated that in the morning she frequently felt "blue," "that life was hardly worth living" and that she seemed to be exhausted. There were no significant cardiac symptoms and examination of the heart gave objectively negative results. The systolic blood pressure in millimeters of mercury was 140 and the diastolic blood pressure was 80. A diagnosis of depression was made. Following administration of 20 mg. of benzedrine before breakfast the patient's condition was remarkably improved. Exhaustion disappeared completely and she felt that the day was not long enough for doing the things she wanted to accomplish. The patient was advised to continue to take benzedrine in amounts of 20 mg. before breakfast, under the care of her physician. The dose was subsequently reduced to 10 mg. The improvement originally noted continued, but about two months after the patient had begun to use the drug retrosternal discomfort and dyspnea developed, symptoms interpreted by her physician as being due to coronary sclerosis. The blood pressure was 180 systolic; the diastolic pressure was not recorded. Benzedrine was discontinued.

CASE 6.—A man, aged 46, came to the clinic because of marked fatigue, abdominal discomfort and mushy stools. He was so exhausted that it was difficult for him to force himself to work for several hours and many simple routine duties required great effort on his part. Physical examination gave essentially negative results and extensive roentgenologic and laboratory examinations did not reveal any abnormalities. A diagnosis of chronic exhaustion and irritable gastro-intestinal tract was made. All symptoms were relieved following administration of benzedrine. By using 10 mg. before breakfast for four months, the patient continued to note the remarkable improvement that he had experienced originally. At the end of this period of four months he had several attacks of severe pain in the chest, which he related to his heart. Although objective examination of the heart by a competent cardiologist gave negative results, it was felt advisable to discontinue the use of benzedrine.

DOSAGE

Benzedrine was administered orally to our patients in doses of from 10 to 20 mg. before breakfast and frequently the amount was given again at noon. When the drug is taken after noon, insomnia usually results. It has been our experience that, if the condition of a patient fails to improve with one of the doses noted, he will not be benefited ordinarily by larger amounts of benzedrine. Many of the patients with exhaustion and depression whom we have observed, and who have taken benzedrine over a period of weeks or months, have found that they were able to reduce the dose to as little as from 2.5 to 5 mg. before breakfast, with continuation of good results. In other cases 10 mg. in the morning and from 2.5 to 5 mg. at noon will maintain a favorable effect. Occasionally patients find that intermittent use of the drug proves more satisfactory than continuous administration. One fortunate quality of benzedrine is that the effects of its administration almost always can be determined in one day. If there is no beneficial effect from its administration before breakfast and lunch on one day, it appears useless to administer it over longer periods.

Benzedrine does not appear to be toxic in the doses that should be utilized clinically. Hartung and Munch [1] found the minimal lethal dose of the hydrochloride of benzedrine to be 25 mg. for each kilogram of body weight of rats and rabbits.[17] Solomon and his associates [8a] have given as much as 160 mg. a day for three weeks to a man without apparent harmful effect, and Davidoff and Reifenstein [14] have administered 200 mg. in one day to a patient without severe reaction.

COMMENT

Although the initial results that follow the administration of benzedrine to patients who are in states of chronic exhaustion and depression are favorable in a high percentage of instances, it is obvious that continued use of the drug lessens its effectiveness. Thus, our studies show that although the initial effects of the administration of benzedrine are favorable to about 70 to 80 per cent of patients who are in states of exhaustion that are not due to organic disease, and to about the same percentage of patients who are in states of depression, the percentage of favorable effects decreases significantly if administration of the drug is continued for weeks or months. This is in sharp contrast to the results of the treatment of narcolepsy, reports of which indicate that it continues to respond uniformly and favorably to administration of benzedrine for as long as three years. If the results of our studies of the continued administration of benzedrine to patients who are in states of chronic exhaustion or depression are confirmed, it will become apparent that the usefulness of the drug in treatment of these conditions is substantially limited. Observations over longer periods of time than those which we are reporting may show still further limitation of the use of benzedrine.

It is probable that eventually benzedrine will be found to have its greatest value in the treatment of chronic exhaustion or depression when it is used temporarily or perhaps intermittently. While it appears to us that in states of exhaustion benzedrine may simply decrease awareness of fatigue, we are uncertain whether this is the result of stimulation of the central nervous system or of sympathomimetic activity. From our experience it appears that the field of usefulness

16. Observations on elevation of blood pressure:
O'Connor, D. M.: Benzedrine, Brit. M. J. **1**: 43 (Jan. 2) 1937.
Peoples, S. A., and Guttmann, Erich: Hypertension Produced with Benzedrine: Its Psychological Accompaniments, Lancet **1**: 1107-1109 (May 16) 1936.
Anderson, E. W., and Scott, W. C. M.: Cardiovascular Effects of Benzedrine, ibid. **2**: 1461-1462 (Dec. 19) 1936.
Guttman, Erich: Some Psychiatric Observations in Arterial Hypertension, Proc. Roy Soc. Med. **29**: 1389-1391 (Sept.) 1936.
Fisher, J. H.: Cardiovascular Effects of Benzedrine, Lancet **1**: 52 (Jan. 2) 1937.
Tovell.[3]

17. Since this paper was presented, W. E. Ehrich and F. B. Krumbhaar (The Effects of Large Doses of Benzedrine Sulfate on the Albino Rat: Functional and Tissue Changes, Ann. Int. Med. **10**: 1874-1888 [June] 1937) have reported studies on the effects of benzedrine sulfate on the albino rat. They reached the conclusion that "the minimum lethal dose of benzedrine sulfate given subcutaneously to rats is from a hundred to a thousand times per kilo the usual therapeutic dose given man orally. The greatest nontoxic dose, i. e., that which fails to produce transient variations, appears to be from 2 to 5 mg. per kilo, in other words about 10 to 50 times per kilo the usual human therapeutic dose."

of the drug in the conditions just named has been gradually narrowed. It is of interest to note that the effects of administration of benzedrine vary widely when it is used in treatment of apparently similar clinical conditions. It seems impossible, therefore, to predict results in any specific instance; only by actual trial can one determine effects.

While the usual initial dose of benzedrine given our patients was from 10 to 20 mg. twice daily, many of them noted that as little as from 2.5 to 5 mg., taken once or twice daily, was adequate. Such relatively small amounts may eliminate or reduce unpleasant effects. Inexplicably, two of our patients, one of whom had chronic exhaustion and the other depression, have continued to feel well for several months after discontinuing the use of benzedrine. This suggests that improvement following use of the drug may not be the effect of benzedrine entirely.

Because some of the startling results which follow administration of benzedrine have been widely commented on in the medical and lay press,[18] the drug has rapidly acquired a vogue for all sorts of conditions. People have kept themselves awake and alert for unreasonably long automobile drives and students have utilized the drug, in many instances unwisely, for stimulation and acceleration of mental processes during examinations. In such instances more common sense and less benzedrine are ordinarily advisable. It is worthy of note that Blackburn,[19] in a study of forty-eight persons, many of whom had disturbances of emotion and mood, reported that these persons, following administration of small doses of benzedrine, increased the score obtained in an intelligence test by an average of 8 per cent. It is also of interest to note that some persons who have indulged in too large quantities of alcohol may find that the characteristic morning "hang over" is greatly benefited by benzedrine.

The indiscriminate use of benzedrine cannot be too severely criticized. It is never advisable, in states of exhaustion, to substitute its use for careful search for the causes of the exhaustion and the correction of them if this is possible. While, as far as we know, toxic effects from administration of benzedrine have not been noted, the possibility that they may occur must be considered. It should be particularly emphasized that benzedrine is a stimulant and therefore that it probably does not fundamentally and permanently alter a psychotic disorder or a state of chronic exhaustion or neurosis. Whether it is logical and safe continuously to stimulate an individual who presents such a disturbance is a question which cannot be answered at present. We feel that until further observation is made it probably will be unwise to recommend the continuous use of benzedrine except to patients who are less than 60 years of age, who present no evidence of hypertension or cardiac disease and who can be closely observed by a physician.

SUMMARY

The immediate effects of oral administration of benzedrine to a group of 100 patients in which, after careful examination, diagnoses were made of chronic exhaustion, depression and psychoneurosis, were beneficial to approximately 80, 70 and 46 per cent respectively. In some instances the results were spectacular.

The effects of the continued administration of the drug were less favorable. Of the patients initially benefited, about 50 per cent who had chronic exhaustion and 25 per cent who had depression continued to receive benefit for periods of from one to eight months.

Benzedrine is a stimulant and therefore apparently does not fundamentally and permanently alter a psychotic disorder or a state of chronic exhaustion. Whether it is logical and safe continuously to stimulate individuals who present such disturbances is a question that cannot be answered at present.

18. Simpson, S. L.: Benzedrine, Brit. M. J. **1**: 93 (Jan. 9) 1937. Allen, E. V.: Benzedrine, editorial, Minnesota Med. **20**: 301-302 (May) 1937. Benzedrine, editorial, Brit. M. J. **2**: 1204 (Dec. 12) 1936. Miller, Hyman: Benzedrine Sulfate, editorial, California & West. Med. **46**: 295-296 (May) 1937.

19. Sargant, William and Blackburn, J. M.: The Effect of Benzedrine on Intelligence Scores, Lancet **2**: 1385-1387 (Dec. 12) 1936.

RELATION OF THE FASCIA LATA TO CONDITIONS IN THE LOWER PART OF THE BACK

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The object of this paper is to show what has been learned to date from the results of fasciotomy on patients with lame back and sciatic pain. Early in the winter a general questionnaire was sent out to the members of the American Academy of Orthopedic Surgeons and others asking them to send in the number of patients operated on by them and the results obtained and to make any comments on their observations. Forty-one reports were received, giving data on 340 cases. To these are added seventy-five reports from the clinic with which I am associated, making a total of 415 cases from which to draw conclusions. Of the 415 patients, eighty-four (21 per cent) obtained no relief, seventeen (4 per cent) showed only partial relief and 314 (75 per cent) had complete relief. The symptoms were relieved immediately or after intervals up to one year. The average time before relief took place was about three months.

It is hoped that what has been learned from analysis of the questionnaires will bring out some points which are necssary for arriving at a proper diagnosis and which will make the indications for the operation more specific, although it will probobly be some time before more definite rules of procedure can be laid down.

HISTORY

Several important factors are to be considered in arriving at a diagnosis if one recognizes that fascial pull in the lower extremity has any relation to conditions low in the back. First there is the history of the condition as related to body mechanics before any story of lame back enters the picture. Have there been any postural disturbances? What is the favorite position in bed? Is the patient able to bend over and touch the floor with his hands when his knees are held straight? What positions induce or aggravate the pain low in the back and the sciatica? How are these conditions affected by sitting, standing, stooping, twisting and walking? Most persons who have difficulties in the lower part of the back associated with contracted fasciae latae lie on their sides with the knee or knees flexed. Lying on the back or the abdomen usually makes them more uncomfortable.

The history, of course, should be as complete as possible regarding the many other factors which are

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