BENZEDRINE SULPHATE IN CLINICAL MEDICINE: A SURVEY OF THE LITERATURE

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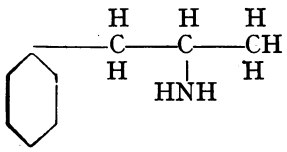
"Some are born great, some achieve greatness, and some have greatness thrust upon them."

History

There is an element of historical curiosity in the reflection that benzedrine, which was born and baptised in America and which is so typically American in its psychology, was the academic brain child of two British scientists. As long ago as 1910 Barger and Dale[1] included this substance in their now classic study on the relationship between chemical structure and sympathomimetric action of amines.

Chemically related to, and pharmacologically comparable with, adrenaline and ephedrine, benzedrine sulphate is systematically known as β-aminopropylbenzene, dl-α-methylphenethylamine or phenyl-l-amino-2-propane. Its formula is $C_6H_5 . CH_2 . CH (NH_2) . CH_3$.



It was first synthetised in 1927 by G. A. Alles[2] of Los Angeles, while searching for a substitute for ephedrine, which would be more economical and easier to prepare. "Benzedrine"* (Reg. U.S. Pat. Off.) is the trade name of Smith, Kline and French Laboratories of Philadelphia, for this chemical compound which was given the nonproprietary name "Amphetamine" by the Council on Pharmacy and Chemistry of the American Medical Association. This name has since been adopted in Great Britain by the British Pharmacopoeia.

It may be doubted whether, with the possible exception of the sulphonamides, penicillin, and streptomycin, any therapeutic agent of modern scientific medicine has aroused such vivid interest in professional circles and in the lay press as benzedrine sulphate. A veritable deluge of literature has been let loose concerning its uses and abuses, its virtues, vices, and potentialities. In the salad days of its therapeutic career, benzedrine not so much achieved, as had thrust upon it, an immense Press publicity, even notoriety: the "Confidence Drug"—"Pep Pills"—"Reach for a Pill instead of a Cocktail." The wave of sensationalism engulfed apprehensive students, tired city magnates, housewives bored with the monotony of their unexciting lives. The wave of sensationalism spread, engulfing psychologists and philosophers, who were intrigued by the vast possibilities of a drug which promised to open up unexplored fields in the study of consciousness.

With the passage of the years and the ripening of experience benzedrine sulphate has found a rationally established place in clinical medicine as a drug with divers and valuable indications, if employed intelligently and with mild scepticism. For many of the published reports have been so striking as to encourage indiscriminate use without proper trial in controlled conditions.

Since January 1, 1939, benzedrine has been obtainable only on the prescription of a registered medical practitioner or the signing of the Poisons Register.[3]

Mode of Action

At a discussion on Modes of Drug Action held by the Faraday Society in 1943[4] interesting suggestions were advanced to explain the mechanism of action of benzedrine, especially on metabolic processes in the central nervous system. The presence of amines such as tyramine produces a marked diminution in the respiration of brain cortex examined *in vitro*. The addition of benzedrine neutralises this inhibition. The fall in brain respiration in the presence of tyramine is not due wholly to the amine itself, but to a product of oxidation of the amine, the corresponding aldehyde. Benzedrine owes its stimulating action in brain respiration in the presence of inhibiting amines to its ability to compete reversibly with amines for the amine oxidase of brain, thereby reducing the rate of formation of the inhibitory aldehyde. It is either very feebly or not at all attacked by amine oxidase, for which it nevertheless possesses a high affinity. The effects of benzedrine *in vitro*, in partially neutralising the inhibition of glucose oxidation by brain due to the presence of tyramine and other amines, take place at concentrations not considerably higher than those having pharmacological actions *in vivo*. Competition between benzedrine and other amines for amine oxidase occurring according to the laws of mass action, it follows that the influence of benzedrine may be exerted in the body at much

* Benzedrine carbonate was introduced into medicine in 1932 as a nasal vaso-constrictor (Benzedrine Inhaler). Amphetamine sulphate is issued in the U.S.A. by Smith, Kline and French Laboratories as "Benzedrine Sulfate Tablets" and in a liquid dosage form as "Benzedrine Sulfate Elixir"; and in Great Britain by Menley & James Limited as "Benzedrine" Tablets.

lower concentrations than have been utilised in experiments *in vitro*. It is suggested that the action of benzedrine *in vivo* is linked with its ability to compete with amines which produce toxic substances by oxidation. The lower the concentration of such amines, the lower the quantities of benzedrine needed to compete successfully with them.

The length of action of benzedrine is approximately eight hours. People of pyknic build appear to tolerate it better than the asthenic. The former react to anxiety with a more parasympathetic type of response, e.g. sensations of a dropping stomach, sweating, slower action of the heart, while the latter respond more sympathetically, with palpitations and tremors. Depending on the predominance of one or other type of response, the effect of benzedrine will be mainly beneficial or mainly unpleasant. In order to get the best out of the drug, the individual reaction should be observed, and the beneficial effect may still be utilised, if its unpleasant autonomic action is neutralised by some other drug such as a barbiturate.[5]

Physiological Actions

1. *Body Temperature*

Doses of 20 mg. or more of benzedrine sulphate may cause a slight rise in body temperature lasting several hours.[6, 7]

2. *Pulse Rate*

The effect of benzedrine on pulse rate is variable. After 10 to 20 mg. an increase of 9 beats a minute for several hours has been observed.[8]

3. *Blood Pressure*

In oral doses of less than 20 mg. benzedrine sulphate has little effect on blood pressure.[9, 10] Twenty mg. by mouth has generally been considered the minimal pressor dose, the effect usually beginning within 15 to 30 minutes after administration and reaching its peak within 1 to 3 hours. Return to the original level occurs within 5 to 8 hours. On subcutaneous or intramuscular injection the pressor effect is more marked, more rapid, and more evanescent,[11, 12] When the drug is administered over long periods, tolerance to the pressor effect is frequently developed.

4. *Respiration*

In man, benzedrine sulphate in therapeutic doses has little or no effect on respiration, with possibly a slight tendency to decrease in rate and compensatory increase in volume.[13]

5. *Blood Picture*

Particularly after large doses of benzedrine, the blood count is often greatly increased, apparently due to mobilisation of blood cells from the splanchnic area,[11] the white blood count being more affected than the red. When the drug is administered over prolonged periods, no demonstrable change results.[14]

6. *Blood Chemistry*

Benzedrine induces little change either in the blood sugar (with, perhaps, a tendency toward increase[9]) or in non-protein nitrogen.[15] The acid-base balance of the blood is not appreciably changed by 10 to 20 mg. under normal or anoxic conditions.[16]

7. *Gallbladder*

Benzedrine retards the evacuation of the gallbladder if a fatty meal is given two hours after its administration.[17]

8. *Electrocardiogram*

In therapeutic doses benzedrine causes no significant changes in the electrocardiogram.[18]

Excretion

The excretion of benzedrine in the urine begins within three hours after oral administration of 20 or 30 mg. About 30 per cent of the base is eliminated during the first 24 hours, 40 per cent over a period of 48 hours.[19]

Clinical Uses

1. *Narcolepsy*

From the historical point of view it is interesting to recall that the first clinical report on the use of benzedrine sulphate was in the treatment of narcolepsy (Prinzmetal and Bloomberg, 1935).[20]

Though this strange disorder first attracted attention in 1880, it remained little understood until World War I, when the problem of the sentinel asleep on duty focused practical interest on the question of pathological somnolence. Before the advent of benzedrine ephedrine had been the favourite treatment, accompanied by moderate success. In 1935 Prinzmetal and Bloomberg[20] revolutionised its therapy by introducing benzedrine in doses of 10 mg. once daily to 40 mg. three times daily, which they described as three times more effective than ephedrine in completely preventing attacks of sleep and in giving practically complete relief from cataplexy. They noted the absence of side-effects such as stimulation of the peripheral sympathetic system, the low toxicity, and the prolonged action. In some of their cases benzedrine completely relieved symptoms which had failed to respond to enormous doses of ephedrine.

To Ulrich[21] two years later oral medication with benzedrine sulphate appeared to be the only satis-

factory method of treatment. No deleterious effects were observed in his cases, and there was no evidence of habit formation. Obesity is a frequent accompaniment of narcolepsy, and it is interesting to note that some of his patients lost weight while taking benzedrine.

Lehrman and Weiss[22] employed benzedrine successfully in treating narcolepsy and cataplexy in a paranoid schizophrenic.

To-day there is general consensus of opinion that for narcolepsy benzedrine is specific and diagnostic. Anything from 20 to 60 mg. daily may be required to abolish the attacks of somnolence, but the requisite dosage, once attained, can be continued for years without increase.[23]

Although the relief obtained with benzedrine is on the whole symptomatic rather than curative, Gorrell[24] was able at times to withdraw the drug entirely in mild cases, when new habits of sleep were formed.

According to Modlin,[25] "the use of benzedrine markedly helps the majority of patients and turns them from social and occupational misfits into useful adjusted citizens. The stimulating effects of this drug on the drowsy cerebral cortex are remarkable and completely alter the life of many narcoleptics."

One of the possible contraindications to the use of benzedrine in narcolepsy was reported by Young and Scoville[26] who administered the drug in two cases complicated by anxiety neurosis, in which it contributed to the precipitation of an active temporary psychosis.

2. *Epilepsy*

Anticonvulsant drugs such as phenobarbitone, which constitute the most useful form of treatment in epilepsy, may in susceptible persons give rise to unpleasant and incapacitating side-reactions such as dullness, irritability, and ataxia. These are at times so exaggerated as to necessitate withdrawal of the drug. There is general agreement in the literature that benzedrine sulphate, taken by mouth, is a valuable adjunct to phenobarbitone therapy, neutralising its sedative, without spoiling its anticonvulsant, effect.[15, 27, 28, 29, 30] The administration of benzedrine permits phenobarbitone to be continued in doses large enough effectively to control the epileptic fits, even though the amount given of the sedative drug would, by itself, produce toxic results.

Cohen and Myerson[15] spoke of benzedrine being specific in the abolition of ataxia and drowsiness which complicated a course of phenobarbitone medication in fifteen patients. In many cases benzedrine can be omitted after a few weeks, while in others it appears to be required permanently. There is a good deal of controversy whether the drug affects the number and severity of the epileptic seizures. Benzedrine has been successfully used in the management of *petit mal* in children,[30] and impulsiveness and violence in epileptoid children with abnormal encephalograms are reported to yield to the drug in doses of 20 mg. daily[31]. On the analogy of its value in narcolepsy benzedrine might well be very useful in the so-called inhibitory epilepsy (Feiling).[32]

3. *Post-Encephalitic Parkinsonism*

While benzedrine sulphate does not benefit the psychotic manifestations of post-encephalitic Parkinsonism (Reznikoff),[33] a number of authoritative reports in the literature agree that such symptomatic features of the pathological condition as general malaise, drowsiness, lethargy, and depression yield to the drug in doses of 10 mg. morning and midday (Solomon et al.,[34] Critchley[35]). Benzedrine is described as being particularly effective when used in combination with scopolamine or stramonium.[34] The drug appears to have a specific action in abolishing or reducing the number and severity of oculogyric crises, which occur in 3 to 20 per cent of the cases. In Solomon, Mitchell, and Prinzmetal's[34] 28 cases these crises ceased to be troublesome in 93 per cent. Out of Weiner's[36] 24 patients 19 showed definite decrease in the frequency and severity of oculogyric crises, muscular rigidity, dysphagia, lethargy, narcolepsy, and depression under treatment with a combination of benzedrine and stramonium. Hoffman[37] obtained 50 per cent relief in 17 patients exhibiting oculogyric crises with benzedrine in daily doses of 10 to 30 mg. administered together with a drug of the belladonna group. Solomon and Prinzmetal's[38] findings are interesting and significant: of 18 patients treated with from 5 to 60 mg. benzedrine a day 18 showed increased energy, 17 disappearance of drowsiness, 14 decrease in muscular rigidity, 13 increase in strength, and 5 decrease in tremor. Karnosh and Zucker[39] recommend a morning dose of $\frac{1}{6}$ grain of benzedrine in addition to hyoscine or stramonium to produce increased animation and diminution of fatigue. While Solomon, Mitchell, and Prinzmetal[34] found benzedrine ineffective in the arteriosclerotic group of patients, according to Davidoff, Reifenstein, and Chambers[40] this drug constitutes the best treatment for Parkinsonism, including arteriosclerotic cases.

4. *Fatigue and Depression*

It is in the treatment of depressive states, especially the milder types with retardation of physical and mental processes and absence of anxiety or excitement, bringing in their train such symptoms as apathy, lassitude, difficulty in concentration, indecision, irritability, pessimism,

anorexia, constipation, vague abdominal discomfort, and paraesthesiae, that benzedrine has built up for itself a reputation unique in therapeutics. A large number of clinical observations both from general practitioners and from specialists testify to its immediate and often dramatic value in breaking the stranglehold of the depression, restoring "energy feeling," and renewing optimism, self-assurance, increased initiative, appetite for work, and zest for living. Among the conditions benefited by the drug are the mental sequelae of influenza and other acute infectious diseases; depression incidental to dysmenorrhaea and the menopause; depression following child-birth; and the persistent characteristic depression of old age with its self-absorption, withdrawal from social contacts and former interests, and loss of enjoyment of the minor pleasures of life. All these depressive states are potentially dangerous, interfering as they do with sleep, appetite, and the normal activities of life, and because of their serious consequences in the shape of alcoholic overindulgence and contemplated suicide. Wilbur and his colleagues[41] report favourable and in some cases spectacular results in 25 out of 32 patients with the typical complaints of fatigue, lack of energy, and lassitude. Using benzedrine in doses of 2·5 mg. on arising (repeated, if necessary, at 10.30 a.m. and 1.30 p.m.) in 50 cases of mild depression not accompanied by agitation, Rudolf[42] found that those patients were most benefited who were depressed in the morning, but brightened up later in the day. The value of the drug in transitory depressive states of the reactive type in which there is difficulty in meeting a situation is stressed by Eggleston and Weiss.[43] The usefulness of benzedrine in chronic exhaustion was effectively proved in 32 cases by Wilbur and his colleagues[44], one or two doses leading to immediate improvement. In some instances the results are described as spectacular: complete disappearance of exhaustion, marked exhilaration, and increased capacity for physical and mental effort.

Benzedrine is of greater value in the acute toxic or infectious states of depression than in functional states and psychoneuroses or in the prolonged organic conditions. It appears to be more useful in those organic states where no psychosis is demonstrable and where deterioration or personality changes are minimal and non-progressive. In the psychoses it is of value in cases of recent onset due to intoxication, particularly alcoholic. Benefit in the post-infectious and post-traumatic psychoses may be marked. Paranoid conditions of whatever origin are not infrequently aggravated by the drug (Davidoff and Reifenstein).[45,46] The fact that the administration of benzedrine often produces euphoria, decrease in negativism, and increase in accessibility, thus facilitating the management of a case, has been emphasised by several clinicians. Guttmann's[47] remark, "It is a relief to hear such a patient say he feels better, instead of hearing his usual daily complaints," vividly sums up the present significance of benzedrine in the therapy of manic-depressive insanity. Woolley[48] is convinced that benzedrine, properly administered in states of extreme depression and retardation, may on occasion determine the difference between prolonged serious illness and fairly prompt recovery.

That there is a sound basis for using benzedrine in emergencies to tide people over periods of temporary, though acute strain, since it relieves tiredness due to lack of sleep, postpones the necessity for rest, and delays the onset of irritability, inattention, and fatigue, is brought out in the following quotations:

"There are social and personal circumstances where to fall asleep or to suffer with temporary fatigue would be disastrous in a somewhat imperfect world. Under these exceptional circumstances 5 to 10 mg. does no harm and meets a trying situation better than any other chemical of the present-day pharmacopoeia" (Myerson).[49]

"Often the physician is called upon to make an important decision, perhaps a life-saving one, when he is sleepy, tired and emotionally fatigued. Poor results in obstetric and surgical cases may be traced to this factor of mental fatigue; a diagnostic possibility is overlooked, and operation is postponed until morning or a procedure is carried out due to insistence of relatives. The doctor who is called to attend a seriously ill patient, perform an operation or deliver a baby, should take a 10 mg. tablet of benzedrine as soon as he is notified. Within an hour he will be alert, his mind wide awake and his mental and physical skill will be normal. He need have no fear of addiction" (Gorrell).[24] The drug thus possesses vast possibilities in nightwork, since it keeps people awake when there are long periods of inactivity, enabling them to concentrate on their jobs and helping to clarify the brain.[50] Though benzedrine does not actually diminish fatigue, merely stimulating psychomotor activity (Thornton et al.),[51] its subjective effect on fatigue is very real. It is not a substitute for sleep and rest, but only postpones their necessity during exceptional periods of physical and mental stress and strain.

The normal dosage of benzedrine advocated for the depressive states is 5 to 20 mg. daily, administered in one or two doses before lunch. As a rule it is not necessary to give more than 10 mg. at a single dose. If there is no response to 20 mg., an increase in dosage is generally accepted to prove ineffective. Johnson[52] recommends an initial dose of 7·5 mg. after breakfast and 5 mg. after lunch.

This is increased by 2·5 mg. until the optimal level is reached.

5. *Schizophrenia*

Opinions on the value of benzedrine in schizophrenia are divided. That it can be a dangerous drug in this condition is agreed on by a number of clinicians. Sargant and Slater,[53] for example, issue the warning that, though on occasion it will relieve the hebetude and inertia of the schizophrenic, it may do this only to precipitate an unexpected outburst of excitement or to provide the initiative to carry out a murderous attack inspired by the patient's delirium. Davidoff and Reifenstein,[54] on the other hand, report improvement in 40 per cent of 57 cases, treated with benzedrine sulphate alone, either orally or intravenously, or with benzedrine sulphate intravenously in combination with sodium amytal by mouth. The following dosage is recommended: on the first day 10 mg. benzedrine sulphate intravenously, followed next day by 0·1 to 0·2 gm. sodium amytal orally, repeated every hour until narcosis is obtained; on the third day 30 mg. benzedrine intravenously, for two or three weeks. Orally 10 to 30 mg. benzedrine may be given from ten days to three months. The drug appears to be most effective in the treatment of incipient dementia praecox of the catatonic type, and by the intravenous route. It is described as being of value in differentiating between schizophrenic and alcoholic psychoses, and also in rendering the schizophrenic patient more accessible to investigation and to psychotherapy. In Sereiskii's[55] experience some effect is shown during the first few days, followed either by return to the original state or by deterioration. Seven of 21 catatonic schizophrenics treated by Woolley[48] with benzedrine by mouth in doses of from 10 to 60 mg. in aqueous solution (1 mg. per c.c.) either recovered or improved during therapy. Psychotherapeutic access became possible through the improved mental state. Twenty-one of 44 schizophrenics were unaffected by the drug, and 11 were made decidedly worse. Among the more unfavourable responses noted was the precipitation of panics in tense or agitated, depressed or catatonic individuals. In one patient administration of benzedrine precipitated a serious impulsive attempt at suicide.

6. *Alcoholism*

There is general agreement in the literature that benzedrine is a most useful drug in the various stages of alcoholism. The acute alcoholic cycle Miller[56] was able successfully to interrupt with 10 mg. benzedrine orally after breakfast and after lunch in 49 cases out of 56, the average duration of alcoholism being 16 years. Physical and mental "hangover effects" were markedly reduced. Soon after treatment an impressive improvement was noted in awareness, sensory perception, and activity drive. Mood and rapport were improved, patients demonstrating greater co-operation, increased accessibility, and decreased negativism. Basing their observations on a series of over 100 cases, compared with a comparable series of control cases, Reifenstein and Davidoff[57] found that in the acute alcoholic psychoses the length of time necessary for recovery was considerably diminished by the employment of benzedrine, frequently by half, and the number of recoveries was slightly increased. In the protracted alcoholic psychoses tending towards deterioration the results were of very little significance, except in the Korsakov group, where a smaller number of cases required commitment after treatment with the drug. While benzedrine was uniformly effective in the acute phases of alcoholic intoxication, in the treatment of chronic alcoholic addiction it proved uniformly unsatisfactory, except that the depression associated with the latter responded to the drug during an institutional regime. The authors point out that in alcoholic states complicating mental illnesses benzedrine may be of value in differentiating depressive states due to alcohol alone, which are rapidly relieved by the drug, from states of alcoholic depression superimposed on and masking depression of psychogenic origin, which do not respond as readily.

In chronic alcoholism Bloomberg[58] suggests that the employment of benzedrine introduces a sufficient interval of sobriety for psychotherapeutic methods to be instituted. Treating 21 ambulatory cases of chronic alcoholism (these were not asked to avoid parties) with 10 mg. on rising and again at noon, he found that 8 had completely abstained from alcohol since beginning treatment, periods of treatment lasting up to 13 months. Only four are described as total failures, though even in three of these there were short periods of abstinence. If a patient had to fulfil an evening engagement, where drinks were likely to be consumed, an extra 10 mg. benzedrine was given late in the afternoon. Of 55 cases of chronic alcoholism treated by Bloomberg[59] with benzedrine for periods varying from a few weeks to 3¾ years about 25 per cent have remained totally abstinent and between 80 and 85 per cent have undergone significant modification of their drinking habits. By relieving the chronic "hangover" and depression of the chronic alcoholic during the period of withdrawal benzedrine is a useful adjuvant to any form of therapy. The patient is made to feel that something concrete is being done for him. According to the same author[60] benzedrine also successfully smoothes out "mood swings" and gives the patient a "lift" on his bad days. "In benzedrine sulphate," writes Miller,[61] "the medical profession is offered a new

and relatively safe remedy with which to combat habitual alcoholism." Berwald and Williams[62] describe benzedrine sulphate in doses of 10 mg. by mouth as the drug *par excellence* for the headache due to overindulgence in alcohol. Rinkel and Myerson[63] in a series of pharmacological studies in experimental alcoholism found that benzedrine lowers the blood concentration of alcohol, probably by inhibiting absorption from the alimentary tract and by delaying the emptying time of the stomach. Quantitatively it was more effective than paredrine, adrenalin chloride, and atropine sulphate.

7. *Barbiturate Intoxication and Narcosis*

Myerson and Loman[64] suggest the utilization of benzedrine sulphate by intravenous drip (50 mg. at $\frac{1}{40}$ per cent concentration over a period of 1 to 2 hours) in the treatment of barbiturate intoxication. Davidoff and Reifenstein[45] successfully employed benzedrine in combating coma and withdrawal symptoms in barbiturate poisoning, but warned that in cases where respiratory paralysis threatened the toxic effect of the two drugs might be synergistic. Reifenstein and Davidoff[65] used intravenous injections of 10 to 40 mg. of benzedrine to terminate amytal (isoAmylethylbarbituric acid) narcosis.

8. *Avertin Anaesthesia*

Michelsen and Verlot[66] overcame narcosis and the depressor effects of avertin anaesthesia by injecting 20 mg. of benzedrine sulphate. Boyd,[67] administering 10 mg. dissolved in 1 c.c. distilled water intravenously to 12 children after avertin anaesthesia, obtained as the only immediate effect a return of the superficial reflexes. There was definite reduction in the duration of the post-operative sleep as compared with control cases. The majority of the patients vomited profusely after benzedrine.

9. *Morphine Addiction*

Duckworth[68] found the administration of benzedrine "an invaluable aid in combating that physical and mental inertia which is a common factor in all cases of drug addiction when recovering." In his patient, a man of 45 who had been taking 10 gr. of morphine by injection daily for four years, a fortnight after complete withdrawal of morphine, benzedrine was given in doses of 5 mg. twice daily, on rising and at noon. This was discontinued after two months. There was no inclination for the patient to fall on alcohol as a stimulant. "The quick return to physical well-being and mental alertness was most marked." Davidoff and Reifenstein,[45, 46] while regarding benzedrine as a valuable aid in treating morphine psychoses and withdrawal symptoms, issue the warning that this therapy, in some patients at least, might only lead to the substitution of one habit for another. By means of benzedrine in 10 mg. doses Guyot[69] was able to counteract the nausea, vomiting, constipation, fall of blood pressure, ventricular tachycardia, and hebetude produced by morphine in the treatment of coronary occlusion.

10. *Codeine Addiction*

Sereiskii[55] reports the case of a physician who had taken large quantities of codeine for many years and who, during the last few weeks of treatment, was completely satisfied with only 10 mg. of benzedrine a day.

11. *Caffeine Mania*

Sereiskii[55] obtained successful results with benzedrine in two cases of caffeine-mania.

12. *Nicotinism*

Benzedrine in doses of 10 mg. after breakfast and lunch has been described as being of considerable value in combating habitual smoking (Miller).[70] It is relatively safe; its therapeutic effect is sufficient to guarantee complete or partial abstinence in almost every case; and, by creating a mild state of euphoria, it eliminates the much feared withdrawal signs. Miller[71] points out that benzedrine in doses of 10 mg. or more may produce dryness of the mouth and throat, thus increasing the desire to smoke. This can be overcome by reducing the dosage of benzedrine to 5 mg. after breakfast and lunch or by chewing candy or gum to help increase salivation. A $\frac{1}{4}$ or $\frac{1}{2}$ grain tablet of luminal occasionally helps over initial periods of restlessness. Sereiskii[55] agrees that 10 mg. of benzedrine twice daily may cause dryness of the mouth and throat, accompanied by increased urge to smoke, and that the reduction of the dosage to 5 mg. twice a day eliminates this disadvantage.

13. *Disseminated Sclerosis*

Small doses of benzedrine enabled Lehoczky[72] to control spasmodic laughter and weeping in this disease. Brickner and Simons[73] obtained better results in some disturbances of gait with this drug than with ergotamine.

14. *Myasthenia Gravis*

In the hands of Thorner and Yaskin[74] benzedrine (30 mg.) proved a useful adjuvant to prostigmin (five to seven 15 mg. tablets daily) in three of five cases with myasthenia gravis, restricting the former to the early part of the day and then switching to the latter. Viets and Schwab,[75] while obtaining good results with benzedrine in four of five cases of myasthenia gravis, preferred ephedrine as a synergist.

15. *Myotonia*

The response in patients with the atrophic form of myotonia to 5 to 20 mg. of benzedrine a day

in two or four doses is sometimes encouraging.[76] Guttmann and Stokes[77] noted a favourable response in mood and activity to the drug in a case of Thomsen's disease, but the ergograph showed earlier onset of fatigue and loss of the "practice effect."

16. *Electric Convulsion Therapy*

Bailey,[78] utilising benzedrine sulphate, a known cortical stimulant, in an attempt to lower the electrical convulsion threshold in the therapy of mental disorders, found this drug to be effective in oral doses of 10 mg. given one hour before the electrical treatment, so that smaller strengths of electricity could be used. As regards its mode of action, it is likely that it exerts this effect centrally rather than by any accompanying peripheral changes, such as the heightened blood pressure. In two cases there was some post-convulsion excitement. This was never very great and may not have been due to the drug, since such excitement has been observed after convulsions in cases where the drug has not been employed. No other undesirable effects were noticed. Even in a patient with a blood pressure of 210/120 no harm appeared to result with the doses given.

17. *Head Injuries*

According to Coburn[79] "one must do what one can for the patient who remains just below a conscious level and who is on the verge of some pulmonary complication. It seems justifiable to stimulate such a patient strongly with benzedrine in the hope of rousing him sufficiently to prevent a fatal pulmonary lesion."

18. *Infantile Cerebral Palsy*

Benzedrine in the hands of Nichols and Warson[80] afforded symptomatic relief in the treatment of infantile cerebral palsy, but tended to increase irritability.

19. *Problem Children and Enuresis*

In hyperactive, distractive children gratifying results have been reported with doses of 10 to 20 mg. benzedrine, smaller doses being ineffectual. Attention span is increased, and noisy children become more subdued (Bradley).[81] Sargant and Slater[82] attribute to benzedrine a specific effect in relieving recurrent bouts of aggressiveness and destructiveness. Paradoxically, in spite of the stimulant action of the drug, the noisy child becomes more subdued. It is well recognised that nocturnal incontinence occurs only during sleep, enuretic children usually being deep sleepers. It is not an uncommon experience for a child to be guided to the bathroom and back to bed without his awakening. Many clinicians agree that in the sleepy, slow child benzedrine may be a useful systematic stimulant (Braithwaite,[83] Stockwell and Smith).[84] Molitch and Poliakoff[85] reported that in 8 of 22 chronic bedwetters relief was obtained psychotherapeutically with a placebo. Of the 14 boys who failed to respond to placebos 12 (86 per cent) were entirely relieved when given increasing doses of benzedrine, up to 25 mg. daily. It is interesting to note that all 22 reverted to their former habits within 2 weeks after withdrawal of both placebo and benzedrine. When enuresis has been controlled, the dosage of benzedrine may be decreased, and the drug gradually withdrawn or a placebo substituted. Other observers[86] have pointed out that benzedrine controls incontinence during waking hours, suggesting that the drug acts also on the bladder musculature.

20. *Migraine*

Several clinicians have found benzedrine useful in cases of migraine characterised by initial fatigue or dizziness (Nathanson).[87] In Gottlieb's[88] series of 22 patients 8 (36 per cent) had their paroxysms of migraine aborted when the drug was given during the prodromal period. Three patients having frequent and severe attacks became symptom-free when this was taken daily and in divided doses at varying intervals up to every four hours. Benzedrine may be used as a substitute for ergotamine tartrate when this is either ineffective or productive of severe toxic symptoms.

21. *Urticaria*

In the experience of Roberts[89] benzedrine sulphate has proved of value in children with urticaria, fluids and laxatives being properly employed at the same time. "The variable individual factors and the potential toxicity of the drug make the estimation of dosage difficult."

22. *Ménière's Syndrome*

Prinzmetal and Alles,[90] using dextro-, racemic, and laevo-benzedrine sulphates in two cases of Ménière's syndrome, report improvement not associated with a rise of blood pressure. The cortical stimulating action of these compounds was found helpful also in relieving dizziness not due to obvious organic disease in several patients, the majority of whom had hypotension.

23. *Sea Sickness*

The treatment of this condition has always been notoriously uncertain, chiefly because different cases present different symptom-complexes, some a predominant vagotonia, others a predominant sympathicotonia. The majority appear to be amphotonic, combining both elements. Since benzedrine stimulates both the central and the sympathetic nervous systems, the possibilities of its value in sea-sickness have been investigated by a number of clinicians. Hill (1936),[91] of the R.M.S. *Aquitania*, inclined to the view that sea-sickness in men is usually vagotonic, and in women and children sympathicotonic, the latter being

characterised by restlessness, broken sleep, and the occurrence of nausea before vomiting, the former by vomiting unaccompanied by nausea, apathy, drowsiness, headache, and vertigo. Hill (1937)[92] administered benzedrine in doses of 10 to 20 mg. to 82 women and 18 men suffering with sea-sickness. His results were classified as satisfactory (39), doubtful (40), and failures (29). Discussing the last group, the author suggests that in the amphotonic type of case benzedrine by itself, even in the presence of definite signs of vagotonia, may swing the balance towards sympathicotonia, so that the drug should be administered in combination with other remedies, such as belladonna or bromides and chloral hydrate. In some cases with extreme vagotonia the dosage may not have been large enough. The drug is described by Hill as an exception to the general rule that a rapid result is apt to be of short duration. Keevil[93] found benzedrine in doses of 10 to 20 mg. before breakfast, and repeated at noon, effective in the prophylaxis and treatment of sea sickness. Ekerfors,[94] of the Swedish American Line, states that the effects of the drug are noted within half an hour, continued as a rule for 4 to 5 hours and sometimes longer. His 116 cases were divided into three groups according to the chief symptoms presented: vomiting; vertigo in the upright position and vomiting; and vertigo in the upright position only. Of the 28 passengers in the first group 20 responded favourably, and 8 were distinctly or indefinitely improved. Of the 67 cases in the second group 61 were completely relieved of their symptoms, while the vasomotor instability of the remaining 6 was greatly diminished. Of the 21 cases in the last group recovery was complete in 20. Albrecht,[95] in a therapeutic evaluation of benzedrine in the treatment of sea-sickness in 100 cases, writes that, given in proper dosage (15 to 30 mg. daily) and under supervision of a doctor, it is a safe drug for the prophylaxis of this condition. Its use permits the patient to be up and about and to eat his usual food. He cites cases of stewards who during rough weather habitually became sick at the sight and smell of food and whom benzedrine enabled to perform their duties without further nausea or vomiting; also of firemen and oilers who, with benzedrine, were no longer made ill by the motion of the ship and the smell of the oil. Blackham,[96] supporting the conclusions arrived at by Hill and Keevil, adds that benzedrine is contraindicated in excitable persons or in those suffering from insomnia, hyperpiesia, heart trouble, or gastric and intestinal atony. A combination of benzedrine with hyoscine was found by Hill and Guest[97] to protect 72 per cent of British and Indian troops liable to sea-sickness in an assault craft under tropical conditions.

24. *Persistent Hiccup*

At one time the hope was held out that benzedrine in doses of 10 mg., repeated, if necessary, for three doses, was able to relieve, temporarily at least this distressing complication, most often seen after upper abdominal operations, and liable in an ill patient to lead to a dangerous state of extreme exhaustion. Shaine[98] obtained good results with its use in three cases, cessation of hiccupping in a post-operative refractory case being described as spectacular. The initial dose administered was 20 mg., the drug being repeated twice the same day in doses of 10 mg. This prompt effect was attributed to its specific action of relaxing smooth muscle. According to Hamilton Bailey,[99] however, "in true persistent hiccup specific drugs are quite useless. One and all are entirely empirical."

25. *Dysmenorrhoea*

Primary, essential, or functional dysmenorrhoea has always been the despair of the general practitioner and the gynaecologist, the formidable number of antispasmodic and sedative drugs and endocrine preparations used in its relief bearing eloquent testimony to its difficulty of treatment. Some 40 to 60 per cent of women are said to suffer from dysmenorrhoea, many of these leading active business, industrial, and social lives, so that the question of treatment assumes economic importance. Several interesting clinical reports are available which suggest that benzedrine is useful in functional dysmenorrhoea in which other measures have failed. In Taylor's[100] 34 patients 40 per cent were completely and 40 per cent moderately relieved, not only of physical pain, but also of fatigue and depression, by 5 to 20 mg. daily. Benzedrine is described as a valuable drug well adapted to ambulatory patients. The usefulness of the drug in mild cases of dysmenorrhoea is attributed by Larkin[101] chiefly to the stimulation that it gives to the tired or worried patient and to the change of mood that is so characteristic. In severe dysmenorrhoea he found it of very little value. In his group of 134 student nurses with mild or moderate dysmenorrhoea 89 (66·4 per cent) were definitely improved on small doses, whereas of 25 moderately severe or severe cases improvement occurred only in four. Hundley's[102] figures are sufficiently striking to be quoted in full. Treating 186 attacks of essential dysmenorrhoea occurring in 91 working girls, he obtained good results (complete relief by initial dose of 10 mg.) in 114 (61 per cent), fair results (required a further 10 mg. 4 hours later) in 27 (15 per cent), and poor results (medication seemed ineffective) in 45 (24 per cent). Brown[103] agrees that severe menstrual cramps are not relieved by benzedrine. In his

recently published textbook Janney[104] recommends benzedrine sulphate as the most satisfactory of the antispasmodic drugs which he has used in the symptomatic treatment of primary dysmenorrhoea. In his experience 10 mg. administered at the onset of pain and repeated in an hour's time, if necessary, relieves uterine cramps and, in addition, improves the patient's mental outlook. With this dosage (10 to 20 mg.) side-reactions are seldom encountered. Nevertheless, the patient should be warned that wakefulness may occur if the drug is taken after noon. Overdosage may occasionally be followed by nervousness or "jitteriness," which is harmless and passes off in a few hours without treatment. Several gynaecologists recommend that, before beginning treatment, it is advisable to administer a test dose of 2·5 to 5 mg. on one or two days during the intermenstrual period, in order to determine whether the patient is hypersensitive to benzedrine and, therefore unsuited to the treatment. Satisfactory results are reported with a dose of 10 mg. given at the onset of the pain and repeated, if necessary, four hours later. In nervous patients it may be preferable to give 10 mg. on the morning of the two preceding days and on the morning of the first day of the period. The dose can then be repeated, if required, the treatment lasting three or four days.

A new combination of benzedrine sulphate with acetylsalicylic acid and acetophenetidin, known as *Edrisal*, has recently been introduced by Smith, Kline and French Laboratories of Philadelphia. This preparation was used in the treatment of some 200 cases of dysmenorrhoea by Hindes,[105] who reported that a single dose of two tablets provided complete relief of pain in 61·5 per cent and partial relief in 34·6 per cent. More than 96 per cent were thus benefited. A total of 88·4 per cent experienced a sense of well-being, mental depression being relieved in every case. Loss of time from work was reduced 72·5 per cent. No unfavourable reactions to this medication were noted.

26. *Ureteral Colic*

Carroll[106] recommended a combination of benzedrine and atropine in ureteral colic to promote relaxation of the spasmodic ureter, while in the hands of Loman, Greenberg, and Myerson[107] the drug proved useful in renal visualisation, in ureteral spasm, due to calculus or other causes, and for the pathologically contracted bladder.

27. *Obesity*

Obesity is to-day recognised as a physiological condition which frequently becomes pathological and thus constitutes a real danger, actual or potential, to the health of the individual. It may be associated with diabetes mellitus, hypertension, cardiac failure, chronic arterial degeneration, coronary sclerosis and occlusion, hernia, and cholelithiasis. It lowers resistance to respiratory infections, shortens life expectancy, and greatly increases surgical risk. Since many grossly overweight patients lack the necessary self-discipline for strict adherence to diet, medication may have to be resorted to in their case.

Obesity is often due to a defect in the mood which upsets the appetite-regulating mechanism, when increased eating, not representing true hunger, takes place in order to compensate for the disturbed mood. The commonest cause of this disturbance in the appetite is the anhedonia associated with psychoneurosis. Lesses and Myerson[108] have demonstrated the value of benzedrine in obese neurotic persons. Since this drug has a direct effect in depressing the appetite and in increasing physical activity, it is useful in any type of obesity. Forty obese patients were treated for periods of 3 to 9 months with an initial dose (gradually increasing) of 7·5 mg. on rising, 5 mg. at noon, and 2·5 at 5 p.m. There were no toxic signs or symptoms. Cotton[109] recommends 5 mg. on rising, 5 mg. at 11 a.m., and 5 at 4 p.m. This is continued until there is an absence of weight reduction for a period of two weeks. The daily dose even in most resistant cases was not allowed to exceed 30 mg. Treatment was continued in a few individuals as long as 18 months without any untoward effects. Cotton suggests that the drug should only be used as a temporary expedient to facilitate the formation of restricted eating habits for a period varying from two weeks to six months.

In Chrisman and Maury's[110] series of 27 obese patients, who had proved refractory to weight reduction, there were only two failures with treatment by benzedrine in the absence of dietary restrictions. The average weight loss was two pounds per week. The majority of cases reported decreased appetite, increased energy, and improvement of mood.

A large number of clinical reports testify to the value of benzedrine in the treatment of obesity due to overeating in children and adults. Ersner[111] describes it as the drug of choice. Albrecht[112] found that nearly all his 300 patients, treated with from 10 to 30 mg. of benzedrine daily in divided doses, lost the desire to eat between meals and, after withdrawal of the drug, could be put on a special diet. No case of habituation occurred in his series. Rosenthal and Solomon[113] in a controlled study of 22 obese patients found benzedrine more effective in inducing weight reductions than thyroid extract. According to them nothing definite can be stated as to the mechanism of its action, but in addition to its effect on activity, mood, and appetite, they suggest that it may act as a diuretic, preventing the retention of excess

of water in the tissues. Studying the effect and mechanism of weight reduction with benzedrine in obese children, Kunstadter and Necheles[114] conclude that the psychic effects and the depression of gastric hunger mobility can explain the results in treatment. They also found that under the influence of the drug children are more disciplined and follow their diet with greater ease.

According to the *Journal of the American Medical Association* in its section *Queries and Minor Notes* (1943),[115] stressing the fact that benzedrine should only be used under careful supervision of a physician, the depression of the appetite would seem to be the chief action of the drug in the treatment of obesity, since the effect on the basal metabolic rate is neither constant nor significant. The loss of appetite, the increased activity, and the restlessness of the patient are sufficient to account for the weight loss which follows its continuous use. When a patient loses his appetite, he is more likely to follow diet.

On a statistical basis about half the persons with narcolepsy become obese, but only about one-tenth becomes as much as 100 per cent overweight. Cutting,[116] reporting on 21 cases of narcolepsy, believes that abnormalities of hypothalamic function may at times be responsible for unnecessary food intake.

The value of benzedrine sulphate as an adjunct to diet and other measures in the treatment of obesity may thus be summarised: it decreases appetite and helps the patient to follow a diet, possibly also by producing a sense of well-being. Increasing activity, it promotes proper balance between energy output and caloric intake. It educates the patient to new eating habits, so that weight loss is maintained after stopping the drug. It has no appreciable effect on basal metabolic rate.

More recently d-amphetamine—a dextrorotary optically active isomer of racemic amphetamine (benzedrine)—has been introduced in the treatment of obesity with good results. Of 162 persons treated for obesity by Hawirko and Sprague[117] 14 received benzedrine sulphate 5 mg. at 8 a.m. and at 10 a.m. In order to overcome excitability and insomnia of 6 patients d-amphetamine was substituted. For the subsequent patients d-amphetamine was prescribed in doses of 2·5 mg. one hour before each meal. This depressed the appetite sufficiently to enable the patient to follow the diet regimen and at the same time eliminated the discouragement and irritability incidental to rigid adherence to prolonged low calorie diet. When in spite of strict dieting weight remained stationary, the dose of the drug was increased to 5 mg. before the biggest meal and finally to 5 mg. before each meal, making a maximum daily dose of 15 mg. Duration of treatment varied from 2 to 12 months. Of the 162 patients treated unfortunately only 72 persevered with their treatment for more than two months. The amount of weight lost varied in proportion to the number of pounds the patient was overweight, the average being 5½ pounds per month. Six failures were observed, which reduced less than 20 per cent of the number of pounds overweight. Salyrgan is considered a valuable adjunct in the treatment of obesity, especially when there is great water retention.

28. *The Irritable Colon*

According to Ingelfinger,[118] in constitutionally worried or depressed individuals benzedrine sulphate, which is also a mild antispasmodic, can be advantageously combined with belladonna or trasentin. The following doses are recommended: trasentin 75 mg. t.i.d., benzedrine sulphate 5 mg. b.i.d. morning and noon.

29. *X-Ray Visualisation*

Several radiologists (Ritvo[119]) have found benzedrine useful for relaxing or abolishing spasm in the gastro-intestinal musculature, thus facilitating, for example, the X-ray visualisation of structural abnormalities of the duodenum. Myerson and Ritvo[120] administered the drug in doses of 30 mg. for this purpose. It was pointed out, however, by Smith and Chamberlin[121] that this technique might produce churning in the small intestine.

30. *Irradiation Sickness*

Jenkinson and Brown[122] report favourable results obtained in 69 patients with benzedrine in the treatment of "the feeling of sickness with acute general symptoms" which sometimes follows the application of massive doses of X-rays.

31. *"Restless Legs"*

Ekbom[123] quotes the case of a hospital nurse who for 10 years complained of periodic crawling sensations in her legs and thighs, induced by fatigue, but not by emotion (asthenia crurum paraesthetica). At one time she used benzedrine (dose not stated), which she found highly effective, but she did not dare continue with the drug as she began to suffer from palpitation.

32. *Carotid Sinus Syndrome*

Benzedrine sulphate in doses of 10 to 50 mg. daily is described as the most effective drug for controlling the circulatory types of this syndrome, characterised by sudden loss of consciousness and postural control (Solomon and Yakovlev).[124] Robinson,[125, 126] was able to prevent syncope due to a hyperactive carotid sinus reflex by administering benzedrine in doses of 20 to 40 mg., repeated so as to bring the daily total to 60 to 160 mg. The duration of inhibition extended over 3 to 6 hours. Induced seizures were sometimes prevented by the drug, and spontaneous seizures were controlled or reduced in number.

33. *Hypotension*

A number of cases have been reported in the literature of postural hypotension which have successfully yielded to the administration of benzedrine sulphate, usually in combination with paredrine, paredrinol, or ephedrine, in 5 to 150 mg. doses a day.[127, 128, 129]

34. *Heart Block*

Poole and Wilkinson[130] obtained reversion to normal sinus rhythm in a case of complete heart block by giving 2·5 mg. of benzedrine on alternate days.

35. *Analgesia*

According to Buscaino and Pero,[131] 20 mg. doses of benzedrine by mouth or by injection help to relieve pain for 1 to 12 hours in cases of sciatica, arthritis, and cancer.

36. *Malingering*

The following quotation from H. C. Solomon and P. I. Yakovlev's *Manual of Military Neuropsychiatry*, Saunders, 1944 (page 193) is of interest: "I believe that the use of such drugs as a combination of benzedrine sulfate and sodium amytal would break down the reticence of the malingerer, although I have little personal experience to back up this statement."

37. *Ophthalmological*

Given by mouth, benzedrine sulphate has little action on the eye. Instillation of a 0·25 per cent solution causes definite mydriasis within a few minutes attaining its maximum in under one hour, and disappearing in about 8 hours.[132] The drug has been used in combination with atropine to produce cycloplegia.[132, 133] Intraocular tension is not significantly increased.[134]

38. *Night Blindness*

Benzedrine has been claimed to produce temporary improvement in night blindness due to vitamin A deficiency (Yudkin).[135]

39. *Libido*

Stimulation of libido, probably due to elevation of mood, has been reported by some clinicians.[136, 137]

BENZEDRINE IN WORLD WAR II

That benzedrine played a vitally important part in World War II is evidenced by the fact that under the name "Energy Tablets" more than 72 million benzedrine tablets were supplied in Great Britain alone to the Admiralty, Ministry of War Transport, War Office, and R.A.F. via the Ministry of Supply (approximately the same quantity was supplied to the U.S. Armed Forces), as spectacular, yet safe, emergency measures, and also by numerous tributes in the literature. As the drug raises the level of physical performance in the course of prolonged effort by lessening the appreciation of fatigue, it was considered wiser, when the emergency was acute, to resort to the use of a drug which makes men temporarily immune to fatigue than to abandon the exhausted (Fetterman).[138] On many a dangerous mission benzedrine helped tired men to win the battle against sleep, when they could not be replaced by rested reserves. "As the result of extensive laboratory and field investigation of the value and limitations of benzedrine, it has been determined officially that this drug is the most satisfactory of any available in *temporarily postponing* sleep when the desire for sleep endangers the security of a mission," writes Major-General David N. W. Grant.[139] "The responsibility for the tactical use of benzedrine rests with the commanding officer, who must decide when the situation demands it. Distribution and administration, however, is the responsibility of the medical officer. When it should be used, how much is needed, and what the effects will be are matters of interest to every member of a tactical organisation. . . . The effect of benzedrine upon a person ready to fall asleep is to restore his alertness and produce a sense of well-being and confidence without impairment of judgment. . . . Since benzedrine does not provide rest, but merely conceals the need of it, sleep following a 'benzedrine alert' preferably should be of such duration that the accumulated fatigue is completely relieved. . . . Properly employed, benzedrine will give an army a few extra man-hours of fighting at the time they are most needed." Benzedrine "stimulates dynamic energy, postponing the desire for sleep, and enables continuation of performance beyond the point at which physical fatigue would be overwhelming."[140] The value of benzedrine in fighting fatigue and heightening combat efficiency during prolonged battle was confirmed in the Spanish Civil War by the psychiatrist Emilio Miro.[141]

The following quotations from "A Guide to the Preservation of Life at Sea after Shipwreck," M.R.C. War Memorandum No. 8, 1943, pay tribute to the value of benzedrine for shipwrecked personnel:

"Energy tablets (1) lessen feelings of fatigue and exhaustion, promote alertness, raise the spirits, and prolong the will to 'hang on' and live; (2) prevent sleep. These effects take about an hour to come on, and they last for several hours, but repeated administration cannot prolong the effects for more than a few days." The warning is issued that the tablets should not be given to wounded men, to excitable or hysterical men, nor to those whose minds are wandering.

Test Dose

Since there is a wide variation in individual

response to benzedrine, there is concensus of opinion in the literature on the advisability of beginning treatment with a test dose not exceeding 2½ to 5 mg., and, if no ill effect is apparent on careful supervision during the test period, of increasing this dosage cautiously and progressively. The first few doses will usually be sufficient to determine whether or not a patient is susceptible to the drug and the correct dosage for his or her requirements. For X-ray visualisation a test dose of 5 mg. is recommended. Overdosage may be controlled by mild sedatives such as the barbiturates. In cases showing any tendency toward insomnia benzedrine should not be given in the later afternoon or evening. Occasionally patients with depressive states after prolonged administration of the drug appear to become insensitive to its beneficial effects. This can be quickly remedied by withdrawing the drug and resuming it after a certain length of time.

Contra-Indications

The following major contra-indications are mentioned in the literature to the use of benzedrine: severe hypertension, coronary artery disease (or other serious heart disease), and manic excitement. The drug should be administered with caution in the severer forms of vasomotor instability, in wide daily variations in blood pressure or pulse rate, in insomnia and anorexia, in homicidal or suicidal patients, in agitated depressive states, and in cases of proven idiosyncrasy.

Safety and the Question of Addiction

The great preponderance of competent clinical opinion favours the view that the incidence of undesirable reactions complicating benzedrine therapy in normal dosage range is negligible and that the few cases reported in the literature are usually traceable to indiscriminate or unsupervised use. "Occasional reactions may occur," writes Pelner,[142] "including headache, restlessness, insomnia, irritability, palpitation, and a disturbance of bowel habit. However, it is necessary to state that these reactions are exceedingly rare, and are merely mentioned to call attention to their rarity." "When used in the proper manner, benzedrine has no apparent permanent deleterious action. All ill effects noted thus far have been largely of minor character and only temporary," writes Ulrich[143] on the strength of his experience in treating patients with maintenance doses of the drug for two years. Rosenberg,[144] giving benzedrine in daily doses of 15 to 25 mg. for periods varying from 1 to 9 months, found unpleasant reactions to be rare and transitory, controllable by sedatives and other measures. Norman and Shea,[145] quoting the case of an alcoholic aged 49, who was admitted to hospital with acute somatic, visual, and auditory hallucinations of 4 months' duration and who had been taking benzedrine in steadily increasing doses—daily maximum 250 mg.—for 5 years, believe that psychoneurotic patients and alcoholics are prone to become addicted to the use of benzedrine. Dermatitis (pruritic lichenified) as a complication is mentioned by Kauvar and his colleagues.[146] Davies[147] reports the occurrence in a student of acute aplastic anaemia following, though not necessarily attributable to, self-administration of 190 mg. in 19 days. Severe cardiovascular collapse occurred after the last dose. The patient recovered and was restored to normal health. In a case recorded by Smith[148] of a student who dies suddenly after taking only 30 mg. of benzedrine, there is considerable doubt as to the role which the drug played in the causation of death. Autopsy failed to reveal any abnormalities. Apfelberg's[149] patient became comatose for 36 hours after taking 140 mg., but made an uneventful recovery. A large number of convincing clinical reports confirm the fact that benzedrine may be safely administered over prolonged periods of time. According to Myerson[49] "long-continued use of the drug in considerable dosage (30 to 50 mg. daily) does not seem to produce ill effects. . . . There are no injuries to personality or intelligence, such as take place with the narcotic drugs."

Administering benzedrine in daily doses of at least 70 mg. to three narcoleptics for 20 to 32 months, Bloomberg[150] in exhaustive tests encountered no significant abnormality.[11] The temperature, pulse, and respiratory rates were normal throughout. There was no increase in basal metabolic rate and no rise in blood pressure. There was no evidence of damage to kidneys or liver. General physical and neurological examinations were entirely negative in all cases. No cutaneous manifestation or gastro-intestinal upset occurred." In one of Bakst's[151] patients, who had been taking 15 to 30 mg. of benzedrine daily for approximately 9 years, "no remarkable effects of the long-continued usage of the drug could be demonstrated, nor were any perceptible changes noted when the drug was discontinued." Gorrell[152] reports the case of a narcoleptic who for a period of two years took 80 to 100 mg. of the drug daily without any ill effects. Solomon, Mitchell, and Prinzmetal[34] record the remarkable story of a patient with Parkinson's disease, who took as much as 160 mg. a day for 3 weeks without apparent harmful effect. A manic-depressive patient, who had taken the astonishingly large quantity of 350 mg. in a single dose, recovered after admission to hospital and the administration of barbiturates (Ehrich et al.).[153] An interesting case is reported by Shorvon[154] of a psychopath aged 35, who had consumed from twenty-five to

thirty 5 mg. benzedrine tablets daily for many months periodically over 4 years. The only apparent withdrawal symptoms were increased restlessness and insomnia, well compensated by barbitone. There were no apparent physical changes. It is emphasised that, although the patient was abruptly deprived of the drug when entering hospital, he did not miss it at all. The warning note sounded in an editorial in the *Journal of the American Medical Association* (1938)[155] that the use of benzedrine over long periods is "certainly not without danger, particularly to the circulatory system," prompted this comment from Lesses and Myerson:[156] "As to addiction, the drugs to which human beings become addicted are the narcotics. There is no evidence in the entire literature of medicine that stimulants become habit-forming." In his clinical experience with benzedrine for more than two years in a very large number of cases Myerson had not seen "a single case of addiction in the sense that a person, otherwise well, now feels it necessary to take the drug habitually and in ascending doses to produce the desired effect." Guttmann and Sargant[157] have found no case of addiction to benzedrine, the only queries being a few instances in patients with abnormal tolerance. "The fact that patients cling to a drug from which they derive physiological benefit cannot be regarded as liability to addiction. The same could be said of insulin or cough mixtures." Just as most diabetics are efficient with and inefficient without insulin, so are some individuals efficient with and inefficient without benzedrine (Shorvon).[154] That benzedrine is not a habit-forming drug and possesses unusually wide margins of safety is confirmed by Sargant and Slater:[158] "Despite popular fears, addiction is very rare and only occurs in the severe psychopath who would have probably become addicted to some drug or other anyway. There are no withdrawal symptoms. Some constitutionally lethargic people demand it, and, if they are benefited by it, may be allowed to remain on it permanently; it is probable that in such persons it has a real part to play in remedying a constitutional inadequacy of the autonomic system or of bodily metabolism."

ADDENDUM

In an interesting study on the effects of amphetamine upon the performance and symptoms of anoxæmic airmen, R. C. Browne, (*Brit. med. J.* June 8, 1946, *1*, 870) found that 15 mg. amphetamine produced a consistently small, but technically insignificant, improvement in performance, reducing the incidence of sleepiness by nearly three times, but having no beneficial effect upon the other symptoms of anoxæmia. "There is, however, an element of 'what is gained on the swings is lost on the roundabouts', in that amphetamine may increase visual symptoms, headache, and euphoria."

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COMMON CASES SEEN IN THE V.D. DEPARTMENT

By EVELYN GOURLAY, M.D.*

About 80 per cent of the cases attending our V.D. Department this last year have been finally diagnosed as non-venereal, and only the remaining 20 per cent were actually infected with Syphilis, Gonorrhoea or soft sore.

This large percentage of non-venereal cases, which I think is usually much the same in the return of most women's V.D. clinics, seems to surprise many people, and they may ask why so much public money should be expended on treating such a large number of uninfected cases.

I thought it might be of interest to talk of the problems presented by these non-venereal cases which often give us much more trouble in treatment than the straightforward case of Syphilis or Gonorrhoea. To begin with, when the patients come up often it is by no means certain whether they are or are not infected until tests have been repeated several times. During the war years we have had a great number of Services contacts where the husband or contact has written to say that he is infected and to ask the wife or friend to be examined. Some are obviously infected or show positive pathological results at once. Some appear to be quite free from infection when first seen, and later develop positive signs while being observed.

* Based on a lecture given at the South London Hospital for Women on May 11, 1946.