surely this is a fault of the apparatus and not of the principle of closed drainage.

The usual method of closed drainage operation is to pierce the chest wall with a trocar and cannula, followed by the introduction of a Pezzar catheter. Although Bettman's thoracotome (1933) enables a larger catheter to be introduced, I have mentioned the advisability of rib resection in most if not all cases. The "flapper" tube (Bohrer, 1934) is far too dependent on the gas-tight junction between it and the chest wall to be effective; also it can only cause negative intrapleural pressure during inspiration.

The Tudor Edwards drainage tube is probably the best because it is large enough to drain thick pus and it possesses an internal flange which greatly helps to maintain a gas-tight junction. If the chest wall is tightly closed round the tube and perhaps reinforced by a collodion-and-wool dressing there will be very little leakage. If, however, the tube is connected with a water seal the slightest leak will cancel all the negative pressure, which as a rule is a few inches of water only during inspiration and coughing. I have therefore tried the effect of a more constant negative pressure with my suction apparatus. A constant pressure can be maintained by placing a large bottle, the volume of which is considerable compared with that of the pleural cavity, between the suction apparatus and the large drainage tube. A constant intrapleural negative pressure of 30 mm. mercury should keep the diseased lung practically at rest in the expanded condition. So far I have not treated enough cases to give statistics, but it appears very satisfactory. I believe that in the past we have been afraid to apply sufficient negative pressure to the pleural cavity. I have also had the opportunity to apply 30 mm. mercury pressure to the pleural cavity after

3. I have tried to point out that suction needs analysing into its components of pressure and the volume evacuated with respect to time, in order to suit the particular purpose required.

I have to thank all the surgical staff of the Liverpool Royal Infirmary for allowing me to try out the above methods on their cases. I am also much indebted to Mr. J. L. Mayhook, B.Sc., A.I.C., for his untiring efforts in designing and constructing the pumps that have been used. The present one, which has proved most satisfactory, is a gear pump worked by a universal 1/16 horse-power motor with a pressure gauge graduated up to 30 cm. mercury. The pressure can be adjusted to the required amount by a blow-off device incorporated in the pressure gauge, while the rate of suction is controlled by a rheostat.

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BENZEDRINE: A REVIEW OF ITS TOXIC EFFECTS WITH THE REPORT OF A SEVERE CASE OF ANAEMIA FOLLOWING ITS USE

BY

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Benzedrine is the name given to a synthetic drug (β -phenylisopropylamine) chemically allied to adrenaline and ephedrine and comparable to them in its pharmacological effects. Prinzmetal and Bloomberg (1935) introduced it into the treatment of narcolepsy, as they had found it to be much more effective than ephedrine in this condition. Guttman and Sargent (1937) recently reported further observations on benzedrine of an experimental and therapeutic nature which had been collected since the preliminary communication on this subject from the Maudsley Hospital by Peoples and Guttman (1936). Their investigation was mostly confined to the action of benzedrine on the cardiovascular system and the psychological changes observed. Benzedrine produces a general psychological stimulation, and subjectively this is shown by increased confidence and initiative, and ease in making decisions, but is sometimes combined with a feeling of restlessness. They describe the psychological effects in detail, and further state that medical colleagues and others who have themselves taken benzedrine have found it of definite value in such tasks as lecturing or taking an examination. Their experience is that mild depression accompanied by retardation is the most favourable of all psychological disorders for benzedrine therapy. In conclusion, they warn against the possibility of addiction and are already aware that the drug is obtained without medical supervision. At present benzedrine may be purchased without prescription. As they say, this seems inadvisable with a drug the properties of which have still to be fully investigated. They emphasize the fact that the therapeutic indications for the use of benzedrine, apart from the treatment of narcolepsy, have not yet been formulated exactly.

Anderson and Scott (1936) have reported the cardiovascular effects of benzedrine. The patients selected for

A portable continuous negative pressure apparatus.

a lobectomy had been performed by Mr. Hugh Reid for the first week after operation. During this time there was no effusion and practically no bleeding, while the general condition of the patient was excellent. I believe that this pressure helped to prevent collapse of the remainder of the lung with the necessary sequel of pleural effusion or empyema. This complication of lobectomy was discussed at a recent meeting of the Association of Surgeons, but no effective preventive measure was suggested.

Summary

1. The value of suction suprapubic and closed empyema drainage has been confirmed.
2. An attempt has been made to construct a suitable negative pressure apparatus for the after-treatment of suprapubic cystotomy, empyema, and lobectomy.

the study were mild neurotics and psychotics, but were physically fit. The drug was given in amounts ranging from 10 to 30 mg. A certain number of normal subjects were also investigated. Pallor, flushing, palpitation, and both increases and decreases in the pulse rate and blood pressure were noticed in some of those receiving benzedrine, and in six recorded cases the effects included collapse, multiple extrasystoles, heart-block, and pain in the chest radiating into the left arm. In a case of involutional depression with paranoid ideas, severe cardiovascular effects of the administration of benzedrine were observed. After some mild preliminary symptoms over a few hours, this patient suddenly collapsed. The pulse rate was slow (56), and examination showed a 1/4 heart-block with an occasional extrasystole. Gradual recovery ensued during the following twenty-four hours. The patient's cardiovascular system on admission showed nothing abnormal, nor was there anything to indicate the likelihood of the severe reaction induced by the drug. Those authors quote Myerson and Ritvo (1936), who reported a severe reaction with collapse in one of their patients. Myerson, Loman, and Dameshek (1936), recording the results of administering 9 to 50 mg. of benzedrine subcutaneously to eighteen mental patients, state that "slight cardiac arrhythmia appeared in four cases. This was either of the sinus type or due to extrasystoles." Their intensive investigations demonstrated marked effects on the cardiovascular system and included a variable rise in the red and white blood counts without change in cell volume or haemoglobin content. Anderson and Scott conclude that until more precise knowledge of the cardiologic effects of benzedrine are obtained caution should be exercised in the administration of doses of 10 to 20 mg. or more, particularly in elderly subjects and because detailed cardiologic investigation of the effects of the drug appears desirable.

In an annotation on Anderson and Scott's report the *Lancet*, in the same number, comments: "If benzedrine does all that is claimed for it already, it is pretty certain, if used repeatedly, to produce some undesirable effects as well." That journal also referred to Myerson, Loman, and Dameshek (1936a), who mention a mysterious and astonishing polycythaemia—ten million red cells per c.mm.—produced on one or two patients by a daily dose of 40 mg. for ten days.

J. H. Fisher (1937), referred to the article of Anderson and Scott. The effect of benzedrine on normal persons was investigated at the Southend-on-Sea General Hospital on eight members of the resident staff. All of them showed a moderate rise of blood pressure, which returned to normal after four hours. The pulse rate in the majority of cases showed a slight increase after half an hour, but later was slowed in all individuals, and was slowest one and a half to two hours afterwards, when the blood pressure was highest. The slow rate while sitting was very unstable, for the least exertion caused a great increase. The only unpleasant feelings noted were by two individuals who on standing up had a transient feeling of faintness. The pulse rate in both had suddenly increased to about 130. The euphoria was well marked in all, and after one and a half hours' conversation was at a maximum. The drug was taken in a 30 or 40 mg. dose by the mouth at 8 p.m., and its effects on sleep were well demonstrated. The amount of sleep varied from two to three hours to none at all.

D. M. O'Connor (1937) reported a case where a striking fall of blood pressure and apparent sphincter spasm followed the administration of this drug in ordinary doses

over seven weeks. S. Levy Simpson (1937) in a comment on an annotation in this *Journal* (1936, 2, 1204), where it was stated that the drug also caused a rise in the red and white blood counts, referred to some experiments made by him and B. H. E. Cadness on guinea-pigs (1936) from which they concluded that "ephedrine probably causes extrusions into the circulation of erythrocytes, leucocytes, and platelets from the storage and haemopoietic centres, including the bone marrow." In addition Simpson mentioned that the sphincter disturbance described by O'Connor was also a part of the toxicology of ephedrine.

Sargant and Blackburn (1936) investigated the effect of benzedrine on the intelligence test scores of a large group of patients at the Maudsley Hospital with successful results. No ill effects of their experiments are recorded, except in the case of a young man suffering from a depressive state with anxiety features. He complained of very unpleasant subjective symptoms, an increase of palpitation, and sweating, yet actually he showed a large rise on retesting.

In a recent annotation (1937) the *Lancet* refers to the investigation of Davidoff and Reifenstein (1936), who reported the effects of a ten to fourteen days' course of benzedrine on normal subjects, and on several groups of psychotic patients. The manifestations observed both subjectively and objectively were extraordinarily numerous and varied. Five of the ten normal subjects developed a state of irritable restlessness which they did not relish, and from the case reports it was evident that the increase of activity and efficiency sometimes involved a dangerous degree of disrespectfulness to superior officers on telephones. Solomon, Mitchell, and Prinzmetal (1937) have produced a fair case for its beneficial effect in post-encephalitic Parkinsonism. They found, by contrast, that the drug was of no use in arteriosclerotic Parkinsonism or in psychotic patients with continuous asthenia, and out of their large experience they join other authors in giving warnings against its indiscriminate use. The *Lancet* infers that caution is clearly advisable, especially in the administration of the drug to normal or relatively normal people, as distinct from those with chronic or incurable disorders.

Case Report

The patient was a robust young man of 26 who had previously enjoyed good health and had suffered from no important illness. He was a pharmaceutical student, and was preparing for the final examination. He had seen articles in the lay press on the action of benzedrine, and learnt that the drug was recommended in the medical press for its stimulant effect on the nervous system, and in particular that it had been found valuable in preparation for examinations. A bottle containing fifty tablets of benzedrine, each containing 10 mg. of the drug, was obtained from a local chemist. From June 15 to 20 last he took two tablets each day, and at first felt no ill effects. On the contrary, he had a marked feeling of well-being and was mentally more efficient, and was more talkative for the first three days. Afterwards he experienced some dryness of the mouth, thirst, and occasional headaches. He worked hard on these days, and remained up until 2 a.m.; sleep afterwards was light, and he awoke easily at 7 a.m., his usual hour. On June 19 he was noticed to be pale, which was attributed to hard study; his colour was usually very good.

The written portion of his examination was held in Cardiff on June 22, 23, and 24, and on each of these days he took only one tablet after breakfast, as he had to travel in daily from a distant country town. Throughout the first part of the examination he had "throbbing headaches" to such an extent that his papers "suffered badly." At this time no

suspicion of any harmful effect from the benzedrine occurred to him. No tablets were taken from June 25 to 28, and sleep even on these days was very restless. On each of the following four days one tablet was taken, and he travelled to London on June 30 for the practical part of the examination, which lasted three days. Severe headaches were again felt daily, and sleep was poor and restless. He returned home by a night train in the early morning of July 3 and, despite a feeling of utter weariness, was unable to sleep during the journey of six hours. At home he was observed to be very pale, and he complained of severe headache and giddiness, thirst, and a dry mouth. Although feeling thoroughly exhausted he was fully awake and unable to sleep.

In the early afternoon of the same day palpitation and a feeling of faintness supervened. He was given a small amount of brandy, when he improved and dozed for a few hours. He became restless again and began to vomit, and suddenly collapsed. The patient was seen at once by Dr. Milne, who found him unconscious and in a severe state of collapse. The pulse was extremely weak, rapid, and irregular, the pupils were dilated, and the skin was cold and moist: he was critically ill for one hour. Vomiting was profuse and of a projectile character for about thirty minutes. He responded fairly quickly to the usual measures of stimulation. Sleeplessness and restlessness were severe for the following three days, despite the use of simple sedatives. Gradual and continuous recovery then ensued, and he is now almost well again. There was no diarrhoea, and constipation was troublesome during the worst stage of his illness. Micturition was normal, except for being more frequent as a result of taking increased fluid for thirst. No haemorrhages occurred throughout the whole course of the illness.

Blood films were examined by Dr. Phillips on July 5 and a slight anisocytosis was the only qualitative change, apart from the poverty of the red cells in haemoglobin.

I saw him in consultation on July 9 and found him to be well nourished but very pale. No retinal or cutaneous haemorrhages were present, and no jaundice. There was slight general enlargement of the heart and fairly natural sounds, except for a haemic bruit in the pulmonary area. The pulse rate was 84, with regular rhythm; and the blood pressure 124 mm. Hg systolic and 50 mm. diastolic. The other systems were healthy, and the liver and spleen not palpable. The urine was normal. Unfortunately, a complete blood examination was impossible on that day. The haemoglobin, however, was 40 per cent., and some films showed much the same qualitative change as in the previous examination. The appearance of the patient corresponded with a red cell count of about two millions.

A full blood count was made a week later, when he was found to have improved in health as a result of the administration of full doses of ferri et ammon. cit. The result was as follows: Red blood corpuscles, 3,080,000 per c.mm.; haemoglobin, 56 per cent.; colour index, 0.9; white blood corpuscles, 5,400 per c.mm. The qualitative change was a little more marked than at my previous examination, and many of the red blood cells now showed polychromasia. No nucleated forms were seen, but there were a few myelocytes.

I saw him again on August 1, when he had improved still further. He was much less pale, and said that he felt almost well again. He was free from headaches, and sleep was good.

Another blood count was now done, with this result: Red blood corpuscles, 4,940,000 per c.mm.; haemoglobin, 94 per cent.; colour index, 0.9; white blood corpuscles, 6,800 per c.mm. The red blood cells were well stained and showed only slight variation in size. No polychromatic staining was seen. The white blood cells were present in normal proportions, but there were no abnormal cells.

Conclusion

A case of acute aplastic anaemia following the self-administration of benzedrine is described. The total amount taken was 190 mg. in the course of nineteen days.

Severe cardiovascular collapse occurred the day after the last dose was taken. Gradual recovery ensued, with restoration to normal health. The patient told me that the drug was being rather much used by students preparing for examinations. It is evident that the sale of this drug should now be strictly controlled by including it in the Schedule of Poisons.

I am much indebted to Drs. R. Baird Milne and Robert J. Phillips for their help in preparing this report.

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PERNICIOUS ANAEMIA WITH DIABETES MELLITUS

BY

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Though the combination of diabetes and pernicious anaemia is well recognized it is sufficiently unusual to merit study. The following case reports are illustrative.

Case I

A carpenter and joiner, aged 43, was known to suffer from pernicious anaemia with achlorhydria. He first came to hospital in July, 1936, when his blood count showed: haemoglobin, 52 per cent.; red cells, 1,900,000 per c.mm.; colour index, 1.3; white cells, 4,900; and a normal differential count. He was given pernaemon forte 4 c.cm. each fortnight and was making satisfactory progress, his blood count in February, 1937, being: haemoglobin, 95 per cent.; red cells, 4,800,000 per c.mm.; colour index, 1. For eighteen months he had been complaining of paraesthesiae of the feet, but there was no weakness, and no physical signs of cord involvement had ever been elicited. The urine had always been normal.

He was one of a family of seven, five of whom were alive and well. One sister had been admitted to hospital three months previously suffering from simple achlorhydric anaemia. Her blood count on admission was: haemoglobin, 25 per cent.; red cells, 1,600,000 per c.mm.; colour index, 0.8; white cells, 9,300; normal differential count. The gastric contents showed complete achlorhydria both to fractional and to histamine test meals, and the Wassermann reaction was negative. She was treated with blood transfusion and massive doses of iron, and was discharged, greatly improved, after three months' treatment, when the blood count was: haemoglobin, 75 per cent.; red cells, 5,000,000 per c.mm.; colour index, 0.75; white cells and differential count normal. The father had died at the age of 69 from heart trouble and dropsy; the mother was alive, aged 74, and suffered from simple goitre.