movable upper back part of the thorax and functions merely as an air cushion.

The positive pressure methods of artificial respiration have been supposed to work partly on account of the distortion of the shape of the thorax and diaphragm and their ability to recoil, and partly due to the nervous reflex by which an inspiration follows an expiration. In the present case the nervous reflex element cannot be helping on account of the nature of the lesion. Various methods have been suggested and used for prolonged artificial respiration in which the patient is put wholly or partly in a box or chamber in which the pressures can be altered (Thunberg,[2] Doe,[3] Steuart,[4] Eisenmenger,[5] Drinker and Shaw [6]). Negative pressure methods are theoretically more physiological, since inspiration is the active muscular phase in natural respiration The most interesting and instructive point about the present case is that positive pressure can be used without apparent ill-effects for a long period. The comfort of the patient and the simplicity and cheapness of the mechanism in the present case is very striking. The patient is in his own bed, carrying on his normal intellectual pursuits, and there are no nursing difficulties.

With a view to future development, the present method is being further investigated. A simple apparatus, which is electrically driven, has already been constructed.

I am indebted to Dr. W. T. Mills for permission to publish the particulars of his patient, and to the patient and his wife for their permission, interest, and help.

REFERENCES

1. Keith, A.: THE LANCET, 1909, i., 825.
2. Thunberg, T.: Abderhalden's Handbuch der bioloischeng Arbeitsmethoden, Berlin, 1927, vol. v., p. 561.
3. Doe, O. W.: Boston Med. and Surg. Jour., 1889, cxx., 9.
4. Steuart, W.: Med. Jour. South Africa, 1918, xiii., 147.
5. Eisenmenger, R.: U.K. Patent, No. 256,974, 1927.
6. Drinker, P., and Shaw, L.: Jour. Clin. Invest., 1929, vii., 229.

PSEUDO-EPHEDRINE IN ASTHMA[1]

BY G. W. BRAY, M.B. Sydney, M.R.C.P. Lond.

ASTHMA RESEARCH FELLOW, HOSPITAL FOR SICK CHILDREN, GREAT ORMOND-STREET, LONDON; AND

L. J. WITTS, M.D. Manch., F.R.C.P. Lond.

ASSISTANT PHYSICIAN TO GUY'S HOSPITAL, LONDON; WILL EDMONDS CLINICAL RESEARCH FELLOW

AT the request of the Therapeutic Trials Committee of the Medical Research Council, we have carried out comparative clinical tests of the therapeutic value of ephedrine and pseudo-ephedrine[2] in asthma. The graphic formula of ephedrine contains two asymmetric carbon atoms, so that two sets of stereo-isomers, making six in all, are possible. Only two occur in nature, *l-ephedrine*, which is the ephedrine in general use, and *d-pseudo-ephedrine*, which is usually known as pseudo-ephedrine. Different species of the ephedra plant contain different amounts of these two alkaloids, and there would be a great saving in cost if they could be used interchangeably. It has hitherto been believed that the action of pseudo-ephedrine is identical with that of ephedrine, but weaker (Chen and Schmidt, 1930).[3] In 1931, however, Chopra and co-workers [4] reported that ephedrine and pseudo-ephedrine were equally effective in the treatment of asthma, but that the latter caused fewer unpleasant side actions. This is the statement we have endeavoured to test.

Ephedrine is of little assistance in a severe paroxysm of asthma or in the status asthmaticus, but it usually aborts a mild attack if taken early, and it usually relieves a moderate dyspnœa. It is therefore a valuable drug in the treatment of asthma, as an intelligent patient can often stave off a severe attack by its use. The unpleasant side actions of ephedrine are familiar to all who treat asthmatic patients. Most common are palpitations, trembling, weakness, sweating, feelings of warmth, chilly sensations, nausea, and vomiting, and the tousse émétique. Less common are nervousness, headache, insomnia, dyspnœa, a tired feeling, thirst, drowsiness, precordial pain or distress, flushing, tingling or numbness of the extremities, anorexia, constipation, diuresis, and dysuria. These side actions are most evident at the beginning of treatment with ephedrine, and it is usual for tolerance to them to be developed and, for the patient to be able to continue the use of ephedrine with relief of the asthma and without the unpleasant side actions. In rare instances, however, toxic symptoms suddenly appear in a patient who has tolerated ephedrine well for months or years.

In the following experiments the relative value of ephedrine and pseudo-ephedrine has been assessed in two ways: (1) by the diminution in the number of attacks produced by continuous administration of the drugs; and (2) by the relief of the actual paroxysm by the administration of the drug at the onset of the attack.

PREVENTION OF ATTACKS

These experiments were carried out by one of us (G. W. B.) at the asthma clinic at the Hospital for Sick Children, Great Ormond-street, W.C. Twenty children, 12 boys and 8 girls, aged from four to nine years, were chosen who had (*a*) had their asthma for at least two years, (*b*) had attacks more or less all the year round, and (*c*) had not previously had hospital treatment. These children were divided into four groups of 5 children and observed during alternate control periods, periods while taking ephedrine regularly, and periods whilst taking pseudo-ephedrine regularly. The dosage employed was a quarter of a grain morning and evening for a child under seven years, and gr. ½ morning and evening for a child over seven years. The mothers were instructed to give an additional tablet whenever an attack threatened. During the control period all the children had two teaspoonfuls of water just coloured with burnt sugar three times a day. No other treatment, anti-asthmatic or otherwise, was given.

Group 1 had four months control period, four months on pseudo-ephedrine, and four months on ephedrine.

Group 2 had four months control period, four months on ephedrine, and four months on pseudo-ephedrine.

Group 3 had two months control period, two months pseudo-ephedrine, two months ephedrine, two months pseudo-ephedrine, two months ephedrine, and two months pseudo-ephedrine.

Group 4 had two months control period, two months ephedrine, two months pseudo-ephedrine, two months ephedrine, two months pseudo-ephedrine, and two months ephedrine.

By this means it was possible to compare the efficacy

[1] A report to the Therapeutic Trials Committee of the Medical Research Council.

[2] The pseudo-ephedrine used in these tests was supplied to the committee by Messrs. Burroughs Wellcome and Co.

[3] Chen, K. K., and Schmidt, C. F.: Medicine, 1930, ix., 1.

[4] Chopra, R. N., Krishna, S., and Ghose, T. P.: Indian Jour. Med. Research, 1931, xix., 177.

of the drugs with each other and with a control period without anti-asthmatic treatment, and at the same time to eliminate any seasonal variations that might occur.

The results are summarised in the accompanying Tables. Each figure represents the number of attacks of asthma during one month. The figures at the base of each group represent the total number of attacks the five children had during the month, and the single figure the total number of attacks the five children had during the control period, the period on ephedrine, or the period on pseudo-ephedrine as the case may be. The marginal figures represent the sex and age of the child.

In summary, the 20 cases during twelve months control period had 49 attacks; in eighteen months on ephedrine they had 78 attacks; and in eighteen months on pseudo-ephedrine they had 52 attacks.

Group 1

—	Control.				Pseudo-ephedrine.				Ephedrine.			
F. 6 ..	1	—	1	—	1	—	3	—	—	1	1	1
F. 8 ..	—	—	—	1	1	—	—	—	1	1	—	2
M. 5 ..	—	1	1	—	—	1	—	—	—	1	—	1
M. 9 ..	1	—	—	1	—	—	1	—	—	1	1	—
M. 7 ..	—	1	1	—	—	—	—	1	—	1	1	1
	2	2	3	2	2	1	4	1	1	5	3	5
—	9				8				14			

Group 2

—	Control.				Ephedrine.				Pseudo-ephedrine.			
F. 5 ..	1	2	—	2	2	2	1	1	—	1	—	1
M. 6 ..	—	1	1	1	1	2	2	1	1	1	1	2
M. 8 ..	1	1	2	1	2	1	—	1	1	2	2	1
F. 7 ..	1	—	—	1	—	1	—	1	1	—	—	1
F. 9 ..	1	—	1	1	—	1	1	1	—	1	1	—
	4	4	4	6	5	7	4	5	3	5	4	5
—	18				21				17			

Group 3

—	Con-trol.		Ps.-ephed.		Ephe-drine.		Con-trol.		Ephe-drine.		Ps.-ephed.	
M. 4 ..	—	1	1	1	1	1	1	—	—	1	—	—
M. 9 ..	1	1	1	—	1	1	—	—	—	—	—	1
M. 5 ..	1	2	1	1	—	3	1	—	1	1	—	1
F. 6 ..	2	1	2	1	1	—	—	1	1	1	1	—
F. 7 ..	—	1	—	1	1	—	—	—	1	1	—	—
	4	6	5	4	4	5	2	1	3	4	1	2
—	10		9		9		3		7		3	

Group 4

—	Con-trol.		Ephe-drine.		Ps.-ephed.		Ephe-drine.		Ps.-ephed.		Ephe-drine.	
M. 7 ..	1	—	—	3	—	2	1	—	—	—	—	1
M. 9 ..	1	2	1	1	—	1	1	1	1	—	1	1
F. 6 ..	—	2	—	1	1	—	—	1	1	—	—	1
M. 5 ..	2	1	1	1	—	1	—	—	1	—	1	1
M. 7 ..	1	2	2	2	1	1	1	2	1	1	—	2
	5	7	4	8	2	5	3	4	4	1	2	6
—	12		12		7		7		5		8	

Or, expressing the figures in the same ratio as regards time, control: ephedrine: pseudo-ephedrine = 100: 107: 73. In other words, whilst the administration of ephedrine did not diminish the number of attacks the administration of pseudo-ephedrine to the same cases and during the same period showed a 27 per cent. reduction of the number of attacks. As regards the severity of the attacks, they were most severe in the control periods, less severe whilst taking ephedrine, and least severe whilst taking pseudo-ephedrine in almost all cases.

Hence one may conclude that pseudo-ephedrine is a more efficacious drug than ephedrine in lessening the frequency of the attacks. Neither drug, if continuously administered, will prevent asthma. In two cases the asthma remained continuous in spite of gr. ½ three times a day in children of seven years. Hence, as both ephedrine and pseudo-ephedrine were used, and the attacks ceased immediately after 5 minims of adrenaline chloride solution had been given hypodermically, neither can replace adrenaline in allaying a severe attack.

One girl of ten years always had sickness and palpitation whilst taking ephedrine but not on pseudo-ephedrine. A boy aged eight years was always made sick by ephedrine gr. ½ but could take the same dose of pseudo-ephedrine quite well. A male of seven years became sick, languid, and listless after ephedrine gr. ½, and complained of palpitation each time. He took pseudo-ephedrine gr. ½ night and morning quite well for two months during which time he had one severe attack lasting four days. Though no sickness or palpitation occurred between attacks, during attacks the tablets made him sick each time for a quarter of an hour, but there was no palpitation. Hence one may conclude that pseudo-ephedrine is less toxic to children than ephedrine in the same dosage.

RELIEF OF PAROXYSMS

These experiments were carried out by L. J. Witts at the asthma research clinic at Guy's Hospital. The standard dose of ephedrine hydrochloride was gr. ½, to be taken as early as possible in the attack and to be repeated at hourly intervals if necessary until grs. 1½ had been taken. If relief was not obtained with this dosage it was rarely possible to improve the results by increasing the dose, on account of the supervention of toxic symptoms. In a few cases, however, the patient had an unusual tolerance for ephedrine, and occasional patients have taken as much as grs. 9 a day with benefit. An analysis of 60 adult patients, who used ephedrine in this way, was as follows:—

28 were relieved by ephedrine and experienced no unpleasant side actions.
23 were relieved by ephedrine but experienced unpleasant side actions.
7 were unable to take ephedrine on account of the severity of the reactions.
2 were totally unaffected by ephedrine.

It was soon found that pseudo-ephedrine had a weaker action then ephedrine. The standard dose of pseudo-ephedrine was therefore fixed at gr. 1, repeated at hourly intervals, if necessary, until grs. 3 had been taken. It was seldom possible for the patient to take a total of more than grs. 4½ of pseudo-ephedrine during an attack without the supervention of toxic symptoms. Reactions to pseudo-ephedrine, when a dosage larger than the standard was employed, were

sensations of cold, shivering, dilatation of the pupils, insomnia, lack of energy, drowsiness, palpitation, nausea and vomiting, and dysuria. The side actions of pseudo-ephedrine are therefore the same as those of ephedrine, but nausea and vomiting are more common.

In the first place the therapeutic effect of pseudo-ephedrine was studied in 21 adult patients, who had previously used ephedrine. In 15 of these 21 patients the asthma was relieved by ephedrine, but there were moderately unpleasant reactions; the remaining 6 patients were unable to take ephedrine on account of the severity of the side actions. The results with pseudo-ephedrine in these 21 cases were as follows:—

3 obtained relief from their asthma without any side actions.
5 obtained only slight relief from their asthma, but there were not side actions. Nevertheless these 5 patients preferred the stronger therapeutic action of ephedrine in spite of its disadvantages.
6 were unaffected by pseudo-ephedrine, either favourably or unfavourably.
7 experienced unpleasant side actions, and did not get the same relief of their asthma as with ephedrine.

These results were disappointing, for it had been hoped that pseudo-ephedrine might be a valuable substitute for ephedrine in patients who had experienced the unpleasant side actions of ephedrine. Of the 21 patients in whom ephedrine had produced mild or severe side actions or had failed to give relief, only 4 preferred the action of pseudo-ephedrine. And of 6 patients, who were completely intolerant of ephedrine, only 1 was relieved by pseudo-ephedrine. The test to which pseudo-ephedrine was submitted in this experiment was severe, for the patients were selected by the criterion that they had experienced unpleasant reactions with ephedrine. Pseudo-ephedrine was therefore prescribed to a second group of 10 cases, of whom 7 had not previously used ephedrine or pseudo-ephedrine, and 3 had been relieved by ephedrine without reactions. The results in these 10 cases were as follows:—

4 were relieved without reaction.
2 were slightly relieved without reaction.
2 were entirely unaffected by pseudo-ephedrine.
2 were not relieved and experienced unpleasant reactions.

The number of our cases is too small for percentages to have any great significance, but it would appear that ephedrine gives relief in about 85 per cent. of adult asthmatics and unpleasant reactions in 50 per cent.; pseudo-ephedrine gives relief in about 60 per cent. of adult asthmatics and unpleasant reactions in 20 per cent. The therapeutic efficiency of these drugs is rather closely correlated with their toxicity, but in a few patients pseudo-ephedrine will relieve the asthmatic paroxysms when ephedrine has had to be abandoned on account of its unpleasant side actions.

CONCLUSIONS

(1) Pseudo-ephedrine given by the mouth was more efficacious than ephedrine in lessening the frequency of attacks of asthma in childhood. (2) Pseudo-ephedrine was less efficacious than ephedrine in relieving the actual asthmatic paroxysm in adults. (3) Pseudo-ephedrine is less toxic than ephedrine, but in large doses it may produce the same unpleasant side actions. (4) Pseudo-ephedrine is worthy of further trial in the treatment of asthma in childhood, and in the treatment of adults who are unable to tolerate ephedrine. (5) Neither ephedrine nor pseudo-ephedrine is as effective as injections of adrenaline in the treatment of the asthmatic attack.

EFFECTS OF TONSILLECTOMY ON ANTITOXIC IMMUNITY TO DIPHTHERIA IN A RURAL POPULATION*

By W. Alfred Buice, M.D., Dr. P.H.

DEPARTMENT OF BACTERIOLOGY AND HYGIENE, THE STATE COLLEGE OF WASHINGTON, PULLMAN, WASHINGTON

In 1916 Tomlin [1] suggested that tonsillectomy might reduce the incidence of diphtheria by eliminating a portal of entry for the bacillus and reducing the number of carriers of the organism. Following this suggestion, a number of clinical writers asserted they had never seen, or rarely had seen, diphtheria in children with tonsils removed. These statements were mere impressions, remembrances, or lack of remembrances, as the case might have been. They did not originate in carefully kept statistics. But in 1924 we began to deal with statistics carefully maintained.

In that year Doull,[2] working in the Baltimore schools, studied 224 cases of diphtheria. Of those 224 cases only 2 had been tonsillectomised. Doull says: "This is a very much smaller number than would be expected in a sample of this size selected at random from the school population. On such a basis the number to have been expected was 26."

In 1927 Collins and Sydenstricker,[3] in an epidemiological and statistical study of tonsillitis among schoolchildren of Hagerstown, Md., reported that diphtheria was found 4·6 times more frequently among children whose tonsils were diseased than among those whose tonsils were removed.

Schick and Topper [4] in 1929 reported that of 300 tonsillectomised children in New York City, 81 per cent. were antitoxically immune to diphtheria, as determined by the Schick test. These children varied from two to twelve years of age. They were charity patients, and came from a highly congested area of the city. On the basis of their findings, Schick and Topper suggested that with more investigation it might be found expedient to resort to tonsillectomy to immunise against diphtheria.

Doull and Herman,[5] also in 1929, made some observations on adults which they have never published. They Schick-tested 232 medical students at Johns Hopkins University, their ages varying between 20 and 29 years. No significant difference was noted in the proportion of immunes among the tonsillectomised and among those with tonsils intact.

Geddie,[6] at the Mayo Clinic in 1930, tested 883 children of Rochester, Minn. Ages varied from one to eighteen. He reported no influence exerted by tonsillectomy on antitoxic immunity to diphtheria.

In 1931 Wheeler, Doull, and Frost [5] reported on a total of 710 children of the Baltimore schools. The children tested varied in age from five to fifteen. These authors reported no significant difference in proportions of antitoxic immunes among the tonsillectomised and among those with tonsils intact.

Shaw [7] Schick-tested 174 Chicago children in 1932. Of 155 in possession of tonsils, 31 per cent. showed antitoxic immunity. Of 19 without tonsils, 33 per cent. were immune.

In 1932 Bigler [8] also tested 470 children of Chicago. The subjects were tested before and after tonsillectomies were performed. Tests made six to nine months after the operations revealed that tonsillectomy and adenoidectomy exerted but little, if any, effect on immunity.

Dudley,[9] in a semi-isolated but not rural community (Greenwich Hospital School) in England, in 1931 reported the frequency of immunes in a tonsillectomised group was twice as large as in a group with tonsils not removed. He thinks that tonsillectomy in itself does not immunise but that in some way it accelerates latent immunisation by the diphtheria bacilli in the environment.

Burton and Balmain,[10] also in England, tested 682 children at Ilford (pop. 131,000) in 1931. They saw no

* The writer is indebted to Messrs. Parke, Davis and Co. for the toxin used in the Schick tests recorded in this paper.