acute catarrhs and during carrier states, we can compare directly the first set of records, covering two years when no systematic treatment was attempted, with the second set, which illustrates the effect of penicillin-spraying, well maintained under the eye of authority, over exactly the same period.

Infection with Staphylococcus aureus

Staphylococcal infections will be considered first because in numbers they predominate. In our previous note on routine detection and exclusion of staphylococcus carriers it was pointed out that only those strains which are actively coagulase-positive, produce alpha-haemolysin, and rapidly ferment mannite constitute a significant menace in the wards. We termed them for convenience Grades A and B, as compared with Grades C and D, found to be practically harmless. Our present figures refer in the main to the invasive A and B strains alone.

It is important also to remember the natural tendencies of staphylococcal nasal infections among hospital populations. Much work on the subject has been done by Miles *et al.* (1944) and Williams *et al.* (1944). They find that there is a marked tendency for persons to be either persistent carriers or persistently free from nasal *Staph. aureus*, and our records agree with theirs. Throughout our routine observations, whenever staphylococcal sepsis appeared in the department practically all those in direct contact with infected cases immediately gave positive cultures from hands, nose, and nasopharynx. After their immediate exclusion these nurses and students submitted to regular swabbing until free. The great majority cleared themselves quickly. But a number, most of whom we had already noted as liable to very persistent carrying, would continue to give positive cultures for many weeks or, in a few cases, months. Therefore in reviewing the results of any systematic local treatment it seems justifiable to consider the "transient" and "persistent" groups separately. In many ways the more transient infections parallel those seen as the "secondaries" following the common cold, whereas the infection of the persistent carrier is akin to, if not actually a true, chronic mucosal infection.

For this reason we have in Table I summarized the records of the transient carriers alone, the untreated above and those regularly using penicillin below. Each group is subdivided numerically according to the days elapsing between infection and permanent freedom.

TABLE I.—*Clearance Times of Transient Staph. aureus Carriers*

	Cases	Days before Freedom from Staph. aureus										
		2	3	4	6	8	10	12	14	16	18	20
No local treatment	50	0	2	5	8	11	10	8	4	2	0	0
Penicillin spray ..	48	3	13	12	9	4	3	1	2	1	0	0

The figures indicate a decided advantage to those using the penicillin spray. Taking the general average, the duration of these transient infections seems to have been reduced by rather more than one-half. It is probably fair to conclude that among the treated individuals the majority found their return to duty accelerated.

If the persistent carriers are recorded in the same way the result is similar. The clearance times of those using penicillin sprays tend to be the shorter.

TABLE II.—*Clearance Times of Persistent Staph. aureus Carriers*

	Cases	Weeks before Freedom from Staph. aureus													
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	14 and over
No treatment	20	0	0	0	0	1	1	0	4	3	2	3	3	1	1	1
Penicillin spray	16	0	0	1	1	2	2	4	2	0	1	1	0	2	0	0

The difference is perhaps not so striking as that seen in Table I, but again there is evidence that the use of penicillin saved the department many lost working days.

Haemolytic Streptococcal Infections

During the four years 38 individuals among the nurses and students had to go off duty owing to tonsillitis or pharyngitis associated with Group A beta-haemolytic streptococcus infection. Some had no local treatment; others sprayed with sulphanilamide powder or penicillin solution. If the duration of local infection is tabulated as before the figures suggest that both forms of spraying have an advantage over no treatment at all.

TABLE III.—*Clearance Times after Str. haemolyticus Infection*

	Cases	Days before Freedom from Str. haemolyticus												
		3	4	5	6	8	10	12	14	16	18	20	22	24
No treatment ..	13	0	0	2	1	3	1	2	0	2	1	0	1	0
Sulphanilamide ..	13	2	2	3	2	1	0	2	0	1	0	0	0	0
Penicillin	12	1	3	4	2	0	1	0	1	0	0	0	0	0

It would seem that penicillin is at least as effective as local sulphanilamide, and can, moreover, claim to be unlikely to produce any toxic effects, however persistently used. For streptococcal throat infections the recently introduced penicillin lozenges should be more convenient and give equally good results.

Summary

Advantage has been taken of the opportunity provided by continuous bacteriological records of the workers in a maternity department covering four years to see what benefit resulted from repeated spraying with penicillin of all staphylococcal and streptococcal nose and throat infections. During the two years of routine spraying the persistence of micrococcus carrier infections has been reduced by about 50%. When infection has been detected in the ward, penicilliin-spraying is therefore now used prophylactically also.

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DOSAGE OF EPHEDRINE IN BRONCHIAL ASTHMA AND EMPHYSEMA

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Ephedrine hydrochloride has been known for a long time as an efficient drug in emphysema and bronchial asthma. Most authors, however, report that in a considerable percentage of cases the drug brings no relief to the patient. This is surprising, as ephedrine, like adrenaline, relieves bronchial spasm in the experimental animal with regularity. It was the purpose of these investigations to find the reason for the variation in the effect of ephedrine in the ephedrine-refractory cases.

It will be remembered that ephedrine, like adrenaline, has many different effects on the human body. Only one of them is the relief of bronchial spasm; others concern the blood pressure, the pulse rate, the width of the pupil, peristalsis, etc. The effect of the drug on the various organs is not always of the same intensity. Thus the circulatory effect or the effect on the nervous system may be so much stronger than the effect on the bronchial spasm that the relief of the latter could be achieved only by a dose so large as to embarrass circulation, which would therefore not be tolerated. Such patients obviously cannot be improved by ephedrine, as the maximum dosage tolerable for their circulation is below the threshold of their bronchial musculature. These subjects tend to have untoward reactions after the usual or even smaller amounts of oral ephedrine, whereas most of them react favourably to ephedrine inhalation. These patients cannot be called ephedrine-refractory, as they react well to the small doses given by inhalation.

There are, however, patients who show no untoward reactions at all, and whose asthma is not improved. The question arises whether the usual dosage is sufficient in these cases. It seemed necessary to use an objective method to follow the ephedrine effect on the bronchial spasm. That such spasm was present could be concluded from the occurrence of the typical wheeze, and the vital capacity was used to measure the effect of ephedrine. It was determined graphically by means of a Benedict-Roth spirometer connected with a drum as used for B.M.R. estimation. The respiratory curve was recorded and the vital capacity taken three times. A suitable dose of

ephedrine was then given and the recording repeated after one hour (former tentative experiments had shown that the maximum effect of ephedrine is usually not reached before 50 minutes and lasts till 2 or 3 hours later). If there was no change in the vital capacity and the wheeze, and if there were no signs of intolerance—tremor, sweating, nausea—another dose was added, and the recording repeated after another hour. If necessary, the whole procedure was repeated once again. As the additional doses of ephedrine follow in hourly intervals their action is superimposed, and the effect is similar to what would have been achieved by a single large dose equal to the two or three consecutive ones. In other cases the ephedrine effect was investigated by giving a tentative dose thrice daily and recording the effect on the vital capacity before and after 2 to 3 days.

Altogether 65 patients suffering from bronchial asthma or emphysema came under observation. In 14 of them the asthma was slight; these reacted to a few small doses of ephedrine and became free from attacks and wheezing for a long interval. They were usually young—most of them adolescents, some between 20 and 30—and their vital capacity was not reduced when they were not in an attack. These cases do not present any problem so far as ephedrine dosage is concerned, and we shall therefore not deal with them here.

Of the remaining 51 patients, 14 were typical severe asthmatics of the younger (extrinsic) type. The other 37 were cases of emphysema. Most of them were over 30 and many over 40. Some had had typical bronchial asthma for many years, but the majority showed a long history of cough or repeated bronchitis, originating 5 to 10 years ago, which was followed later by breathlessness on exertion. In many of these, asthmatic attacks had developed at a late stage of their history, and were apparently not the cause of the emphysema. These 51 patients had one characteristic in common—a nearly continuous wheeze. In most of them, also, a reduction of the vital capacity, radiological signs of emphysema, and an increased reserve air were present. All therefore may be classed as emphysema, although in some of them bronchial asthma could be traced as the principal cause.

In order to compare the ephedrine effect in these 65 chest patients with its effect in other subjects we have also investigated its action in 4 normal persons and 8 patients with heart disease. There is not much change in the vital capacity after the usual dose of 1/2–1 gr. (32–65 mg.). The differences are mostly less than 100 ml., and they lie in both directions. This negative result was to be expected, as Voegtli and Verzár (1945) have shown recently that the vital capacity in normal persons is not influenced by adrenaline. It should be emphasized that all four subjects experienced slight side-effects of ephedrine—tremor and palpitations. This shows that the dosage was near the limit of what was tolerable. The same result has been obtained in 8 patients with heart disease. These patients had been in congestive failure for various reasons some time before, but showed now no external signs of failure. In none was congestion of the jugular veins present, but most of them showed a reduced vital capacity and the chest skiagrams revealed increased vascular markings. They had no bronchitis. Although ephedrine did not influence their vital capacity significantly, the side-symptoms were more pronounced in this group than in the normal subjects.

Patients with Bronchial Asthma and Emphysema

The difference in the reaction of these patients is striking. Although there are a few who feel palpitations or tremors after the usual small doses, the great majority do not, and it is surprising to see how large doses of up to 4 gr. (0.25 g.) are tolerated without any toxic effects. Even prolonged dosage of 3–3½ gr. (0.2–0.225 g.) t.d.s. has produced no ill effects in such patients (as has been found by Middleton and Chen, 1927). The effect on the bronchial spasm, as shown from the increase in vital capacity, is pronounced.

We can divide our 51 patients, according to their response to ephedrine, into four groups: (1) those who respond to doses up to 1 gr.; (2) those who respond to higher doses; (3) those who are hypersensitive to very small doses; and (4) those who are refractory or nearly so to any dosage.

(1) *Those Responding to Doses up to 1 gr.*—The vital capacity increases by 200–400 c.cm. Only 5 cases in our series of 51 reacted in this way, which is the usual reaction seen in light asthmatics—the group we have excluded from this investigation.

(2) *Those Responding to Higher Doses.*—The accompanying table gives the results in 28 patients. In some of them the negative or very slight effect of smaller doses is given in italics beside the larger and effective doses. In the first part of the table the immediate effect of a single dose of ephedrine is recorded; in the second part the effect of continuous dosage over several days. In the 7 remaining cases of this group the clinical improvement was definite, but the effect was not recorded by the spirometer. In some of these cases, after the beneficial effect of ephedrine had been ascertained, it was continued with other treatment, especially inhalation of various substances. Breathing exercises were given in many cases throughout the whole course of treatment. In all these cases ephedrine increased the vital capacity considerably (the average was 518 ml.), and the subjective relief was great. Even an increase of 200 ml. was usually accompanied by easier breathing, and in the case of advanced emphysema the breathlessness on slight exertion improved considerably. The wheeze disappeared in some instances, in others it diminished in intensity, while in yet others it remained unchanged in spite of the subjective relief. It is quite clear from the recorded reaction of these patients to smaller doses that they were quite insensitive to them, whereas they reacted favourably to higher dosage, these latter patients being in a higher proportion than those reacting to smaller doses. It would be interesting to find whether there are special clinical characteristics for this group. While it is impossible to differentiate accurately among such a small number of patients, it can be said that the largest doses were required by patients who were in a severe asthmatic state of long duration or had severe emphysema. Patients with asthma-free intervals usually did not require high dosage, but responded to doses near 2 gr. (0.13 g.).

Table showing Results with Doses above 1 gr.

Case	Date	Normal Vital Capacity derived from Weight	Vital Capacity Before Ephedrine	Dose of Ephedrine	Vital Capacity With Ephedrine
		ml.	ml.	gr.	ml.
1	4/6/45	3,120	*4,250*	*1**	*4,335*
1	4/6/45	3,120	4,250	1½*	4,810
1	13/7/45	3,120	3,850	2*	4,860
2	27/8/45	3,065	2,985	2*	3,225
3	5/2/45	3,480	*2,615*	*1½**	*2,635*
3	7/2/45	3,480	2,450	2*	2,705
4	5/2/45	2,685	*1,890*	*1½**	*2,005*
4	7/2/45	2,685	1,845	2*	2,060
5	17/8/45	3,150	2,535	2*	3,210
6	1/9/45	2,590	1,070	2*	1,360
7	1/9/45	1,790	775	2*	1,200
8	26/11/45	2,520	*1,835*	*1**	*2,060*
8	26/10/45	2,520	2,255	1½*	2,950
9	6/7/45	2,030	*1,690*	*1½**	*1,610*
9	6/7/45	2,030	1,690	3*	1,900
10	27/8/45	2,410	*2,330*	*2½**	*2,500*
10	27/8/45	2,410	2,330	3½*	2,900
11	26/11/45	2,875	2,440	2½*	3,230
12	26/11/45	3,400	1,255	3*	1,875
13	31/8/45	2,875	1,350	4*	1,605
13	3/9/45	2,875	1,590	4*	1,785
14	22/6/45	2,660	*1,415*	*1†*	*1,545*
14	13/7/45	2,660	*1,415*	*1½†*	*1,670*
14	20/7/45	2,660	1,415	2†	1,945
15	4/12/44	2,270	*1,970*	*1½†*	*1,965*
15	11/12/44	2,270	*1,970*	*2†*	*2,400*
15	18/12/44	2,270	1,970	2½†	2,800
16‡	26/10/45	2,280	2,395	2½†	2,815
17‡	29/10/45	4,240	*2,750*	*2½†*	*2,605*
17	2/11/45	4,240	2,750	3†	3,090
18‡	24/8/45	2,875	*2,175*	*2†*	*2,130*
18	27/8/45	2,875	*2,175*	*2½†*	*2,420*
18	31/8/45	2,875	2,175	3½†	2,950
19‡	5/10/45	2,375	1,120	2½†	2,060
20‡	19/11/45	2,210	*1,760*	*1†*	*1,730*
20	23/11/45	2,210	*1,760*	*1½†*	*2,210*
20	26/11/45	2,210	1,760	2†	2,625
21	14/12/45	2,950	2,715	2†	3,065
22‡	14/12/45	2,255	3,070	1½†	3,245
23‡	12/11/45	3,780	3,410	2½†	3,845
24‡	12/11/45	3,020	2,290	1½†	2,640
25	24/8/45	4,065	2,710	1½†	3,560
25	31/8/45	4,065	2,710	1½†	3,685
26	4/1/46	2,805	2,970	3†	3,435
27	4/1/46	3,040	1,825	2½†	2,620
28‡	22/10/45	2,410	1,730	1½†	2,025§
				Average increase ..	518

Experiments with suboptimal doses are given in italics.
* Effect of one single dose. † Continuous effect of t.d.s. doses, usually on the third day of dosage. ‡ Inhalation treatment was given at regular intervals during the whole course. § After six days of 1½ gr. t.d.s. the vital capacity was back to 1,800 and 1,750 ml. Under 2½ gr. t.d.s. it increased again to 2,010.

Acquired Ephedrine Tolerance

In the cases described above the resistance to small doses seems to be genuine, as many of them had never been treated with ephedrine and none of them recently. We have, how-

ever, watched other patients who acquired a tolerance to ephedrine.

When, for instance, a dose of 1 gr. was given thrice daily with good success it was found that after a short time—often after 3 or 4 days—the vital capacity decreased again to its original value. If the dose was then increased to 1½ gr. (0.1 g.) the vital capacity increased again, only to lose its effect after the same interval. (An example for this—Case 28—is given at the end of the table.) In this way the amount of ephedrine had to be increased at short intervals till a dosage was reached (usually between 3 and 4 gr.) at which toxic symptoms, mostly nausea, appeared and prevented further increase. This phenomenon is clearly seen only with three daily doses where effects overlap slightly in the daytime. With two daily doses resistance is not acquired so easily, but except in the case of slight and transient attacks this dosage cannot be relied on to give relief. In such slight cases the attack is often cut off by two or three doses and the drug can be omitted again for good. In those cases, however, in which a continuous wheeze, even of a moderate degree, has developed, a long-lasting ephedrine effect is desirable, and in such cases the acquired tolerance is a great obstacle. Fortunately, the resistance is lost as quickly as it is acquired. When the primary efficient dose becomes inefficient, ephedrine can be omitted without any ill effect, and after a short while (often 3 to 4 days) the previous degree of sensitivity has been restored, and the previous dosage can be given with the same good result.

The tolerance for ephedrine develops very quickly. This could be seen when side-symptoms developed on the first day of treatment. When the first dose given to a patient was near his limit of tolerance he often complained of palpitations or tremor. If these were only very slight the dose was not reduced, and in nearly all cases the symptoms disappeared on the second day. This "first-day side-symptoms" phenomenon became very common in our experience. Similar observations have been made by Althausen and Schumacher (1927) and Hollingsworth (1927).

In the circumstances it does not seem useful to give an efficient dose of ephedrine for longer than about 4 days. Then the dose must be increased or omitted altogether. We found that the latter method is satisfactory in all cases except those which still require an uninterrupted ephedrine effect. Most cases do not, and if the ephedrine is omitted for 3 or 4 days the vital capacity decreases only a little and the condition remains subjectively unchanged. After this the previous dosage can be resumed and a new improvement obtained or, at least, the former maximum vital capacity restored. The procedure can be continued for a long time. Later, when the asthmatic state has been overcome, it can be discontinued, and if a new attack should afterwards occur the same routine can be employed again.

(3) *Patients Hypersensitive to Ephedrine.*—In our series 3 patients were observed who were hypersensitive to doses of less than 1/2 gr. (32 mg.). If necessary these patients can be made tolerant by starting with doses of 1/8 gr. (8 mg.).

(4) *Patients Refractory to Any Dosage.*—Another group of refractory cases comprises those which are not hypersensitive but hyposensitive. Doses of 1, 2, or even 3 gr. have either no influence or only a very small influence, and if the dose is further increased heavy toxic symptoms appear. In addition, small improvements, if achieved, are lost quickly through an additional acquired tolerance. Such cases are not very rare. We have seen 8 in our series of 65 cases.

Discussion

These results present the ephedrine effect as much more complicated than it has appeared till now. The individual variation of the response is greater than to most other drugs, and even in the same subject the response varies with the tolerance which may have been acquired, and possibly with the changing severity of the bronchial spasm. Whereas in slight asthmatic conditions the customary small doses are sufficient in a higher percentage of cases (according to the survey of Chen and Schmidt, 1930, about 2 out of every 3 patients seem to have improved), in our series of 51 *severe* cases only 5 responded to this dosage. Thirty-five patients responded well to high doses, which seem to have been employed in the past only rarely (Middleton and Chen, 1927; Christopherson and Broadbent, 1934). The remainder were either hypersensitive to the drug (3) or refractory (8).

These facts make its use difficult, and they explain why in so many cases no satisfactory results are achieved with a chance dosage. The practitioner will find it difficult to test the sensitivity to ephedrine by means of the spirometer, but in hospital the method could easily be used, and it is suggested that every patient who does not respond to the ordinary oral ephedrine doses should have his vital capacity estimated in order to find out the correct dosage. The advantage of such a procedure is great, as the proportion of improvements under ephedrine increases considerably. Therapeutic measures at our disposal in such severe cases are neither numerous nor very effective, and every possibility should be utilized. These patients, with their breathing capacity often reduced to a minimum that allows hardly any movement, will be relieved greatly by an increase in vital capacity of even 200 or 300 ml.

Compared with this possibility of a success, the side-symptoms which may appear should not act as a deterrent. The symptoms of slight overdosage are palpitations, tremor, nausea (altogether in our series we have only twice seen bladder symptoms—frequency—and once mydriasis which disturbed vision). They have never developed to a degree which was in the least dangerous to the patient, and they often disappeared spontaneously on the second day. If they did not, a slight reduction in the dosage at once led to their disappearance. The blood pressure, which was taken at frequent intervals and often daily, did not show any pathological variations under ephedrine. In these circumstances a slight overdosage can hardly be regarded as dangerous, and should be considered justifiable in view of the possibility of a success. If a practitioner who has no spirometer at his disposal finds no response whatever to doses of 1 gr. t.d.s., it is suggested that he should make use of the higher dosages as described in this paper.

Although we regard oral ephedrine in the correct dosage as very efficient in the treatment of severe cases of asthma and emphysema, it is by no means the only one, and often other drugs, or inhalation treatment and physiotherapy, have to be used instead or in combination with it. It is outside the scope of this paper to comment on these other forms of treatment in detail. It should be mentioned, however, that there is one condition in which oral ephedrine seems of little use—namely, the acute asthmatic attack. In the acute attack quick relief is necessary, and oral ephedrine requires too long to become effective. In addition, particularly high doses seem to be required which are often not tolerated. This fact makes the treatment of the severe asthmatic or emphysematous person very complicated and difficult. If one has succeeded in improving such a patient's chronic asthmatic state considerably an acute attack may intervene which requires other forms of treatment, and one will have to wait till this attack has subsided to continue with the previous regime.

Summary

While some subjects are highly sensitive to the customary doses of ephedrine (1/4 gr.-1 gr.), many patients with bronchial asthma and emphysema are insensitive to them, especially the more severe cases that are in a chronic asthmatic state.

These patients often react well to high doses (2 gr.-3 gr.) and without any toxic symptoms or signs. This is shown by the immediate increase of the vital capacity, the frequent disappearance or diminution of the rhonchi, and the subjective relief.

Ephedrine tolerance is acquired quickly. If it is given 3 or more times daily it loses its effect soon—often after 3 to 4 days. If the dose is increased then, the higher dose will have the same effect as the former small one. If a patient has become tolerant to a certain dosage, and the drug is omitted, he will regain his former response to this dosage usually after 3 to 4 days.

An intermittent treatment with the primary effective dose is therefore suggested. It may play an essential part in the rehabilitation of these patients, who usually are regarded as invalids.

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