labile, the exercise tolerance may be severely limited. The pain is not always immediately relieved by rest, since this relief appears to depend on the return of the heart-block to the resting state. Similarly, the pain may occur at rest with the abrupt slowing of the heart rate due to the onset of heart-block. The history may be very suggestive of an impending cardiac infarction. When the change is from 1 : 1 to 2 : 1 block a cardiogram will not be helpful between attacks, and the fear that the symptoms are due to an impending cardiac infarction will prevent an exercise test being done. Some of these patients must be undergoing treatment with continuous anticoagulants and unnecessarily running the hazards of this therapy. A 2 : 1 block might be missed when alternate P waves are buried in the T waves as in Case 2 (Fig. 2 c). The feeling of panic, probably a manifestation of left ventricular failure (Fowler, 1962), also suggests a psychogenic basis for the symptoms.

The symptoms in patients with a transient or changing heart-block vary from typical Stokes–Adams attacks on the one hand to the unrecognized chest pain and other symptoms described here. When chest pain occurs in a patient with heart-block it is assumed to be anginal and the pain and the block are attributed to ischaemic heart disease. Smith and Zoob (1961) have shown that many cases of heart-block in elderly persons are not due to ischaemia, the cause being unknown. One of the four cases described had clinical evidence of coronary artery disease and another had post-mortem proof. But it cannot be assumed that the heart-block in these patients was due to ischaemia. The chest pain was clearly related to the heart-block itself and not to any coronary disease that might also be present.

Froment *et al.* (1959) state that the pain is anginal because of the characteristic features, particularly the relief with trinitroglycerin. The effect of trinitroglycerin is mentioned only in their patient in whom some ischaemic heart disease was found at post-mortem examination. Assuming that the pain is due to decreased coronary blood flow with the onset of heart-block (Starzl *et al.*, 1955), there is no reason to believe that a coronary vasodilator should be beneficial in such a case. Trinitroglycerin may cause the heart-block by accelerating the auricular rate and thereby produce or aggravate the pain as seen in two of the four cases reported here. Similarly, effort angina due to anaemia may be worsened by vasodilators (Fowler, 1962). Evidence that the pain in these patients is not due to cardiac anoxia stems from observations on Case 1. A 2 : 1 block produced by slight exertion caused severe symptoms but no ischaemic changes in the cardiogram, whereas later severe exertion producing a definite ischaemic pattern was associated with only slight retrosternal discomfort. The abrupt slowing of the heart at the time of increasing venous return with exercise could lead to distension of the heart. This was considered to be the possible cause of the pain in these patients before discovering that many years ago Pierre Merklen (1908) attributed angina pectoris to sudden left ventricular distension.

The other symptoms associated with the chest pain can be attributed to the abrupt slowing of the heart when exercise is increasing the venous return. It has often been shown that adaptation to heart-block occurs so that the working capacity becomes virtually normal (Gilchrist, 1934 ; Campbell, 1943 ; Ikkos and Hanson, 1960), but there is no time for adaptation with the transient changes in rate described here.

Summary

This paper describes the cases of four patients with a syndrome in which chest pain, dyspnoea, palpitations, faintness, weakness of the limbs, and alarm are associated with a transient or increasing heart-block occurring usually on exertion. The symptoms may occur at rest and may be aggravated by trinitroglycerin.

This syndrome is probably common, but the symptoms are attributed to a psychoneurosis or an impending cardiac infarction. The diagnosis is confirmed by a cardiogram taken after exercise. This may be considered unnecessary if the patient is thought to be neurotic, and dangerous if an impending cardiac infarction has been diagnosed.

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TREATMENT OF EXACERBATIONS OF CHRONIC BRONCHITIS WITH AMPICILLIN

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Several different antibiotic regimes have been proposed for the treatment of exacerbations of infection in patients with chronic bronchitis. These antibiotics have been chosen for their activity against *Streptococcus pneumoniae* and *Haemophilus influenzae*, which in the past ten years have become recognized as the common pathogenic organisms isolated from the sputum in an exacerbation (Mulder *et al.*, 1952 ; May, 1953). *Str. pneumoniae* is sensitive to a variety of antibiotics, but it is more difficult to select a suitable antibiotic with activity against *H. influenzae*. Benzylpenicillin is effective only in large doses (Goslings *et al.*, 1961). The acid-resistant penicillins with a phenoxymethyl, phenoxyethyl, phenoxypropyl, or a phenoxybenzyl side-chain show less activity against *H. influenzae* than does benzylpenicillin (Barber and Waterworth, 1962). Streptomycin is effective and bactericidal but has the disadvantages of having to be injected, the possibility of masking pulmonary tuberculosis, and the risk of eighth-nerve injury. The tetracyclines are effective against most strains of *H. influenzae* but are only

*Working with a reseach grant from Beecham Research Laboratories Ltd.

bacteriostatic and side-effects are occasionally troublesome. Chloramphenicol is perhaps the most effective antibiotic available but may cause fatal marrow aplasia.

Therefore, despite the wide range of antibiotics already available, a drug which can be taken by mouth, is bactericidal, has activity against both *Str. pneumoniae* and *H. influenzae*, and is free from serious side-effects would be a most useful addition to the treatment of chronic bronchitis. Ampicillin ("penbritin")—a synthetic penicillin prepared from 6-aminopenicillanic acid—would appear to have many of these characteristics (Rolinson and Stevens, 1961). The results of treatment with ampicillin in the few patients with respiratory infections due to *H. influenzae* so far reported (Lockey *et al.*, 1962; Trafford *et al.*, 1962) have been favourable. We have therefore studied the results of treatment with ampicillin and compared these with treatment with other antibiotics in 35 patients who were admitted to hospital with acute infective exacerbations of chronic bronchitis.

Clinical Methods

All patients admitted to this hospital between November 1, 1961, and April 30, 1962, with an exacerbation of chronic bronchitis who were producing purulent sputum were included in the trial. Chronic bronchitis was defined, as in the Medical Research Council's (1960) questionary, as the production of phlegm on most days for as much as three months in each of the last three years. Patients who were sensitive to any of the penicillins or were unable to take tablets by mouth were excluded; during the trial one patient had to be excluded because of sensitivity to benzylpenicillin. Two patients were excluded because they had lobar consolidation.

A considerable proportion of patients admitted to hospital with exacerbation of chronic bronchitis have already had antibiotic treatment from their general practitioners either on a long-term basis or for a few days at the onset of the exacerbation. For the purpose of this trial it was thought that every patient should start treatment with a new antibiotic on admission, and careful inquiry was made from the patients and their practitioners about previous antibiotic treatment. Patients were regarded as having had previous antibiotic treatment if they had had an antibacterial drug for more than one day in the fortnight previous to their admission.

As the tetracyclines are probably the most commonly used antibiotics in chronic bronchitis, we compared the effects of demethylchlortetracycline with ampicillin in patients who had received no previous antibiotics. In the case of patients who had received antibiotics we compared ampillin (which was not available to practitioners at the start of this trial) with the combination of phenoxymethylpenicillin and streptomycin. Twenty patients admitted to the trial had had previous antibiotics—tetracycline in 17, chloramphenicol in 2, and phenoxymethylpenicillin in 1—so that all patients did in fact receive a new antibiotic on admission.

A week of antibiotic treatment was given, after a specimen of sputum had been obtained for macroscopic and bacteriological examination, as follows:

1. Patients born in a year ending with an even number were given, whether they had previous antibiotics or not, 500 mg. of ampicillin six-hourly by mouth for 48 hours and then 250 mg. six-hourly for a further five days.

2. Patients born in a year ending with an odd number: (*a*) Those who had not had previous antibiotics were given 600 mg. of demethylchlortetracycline twice daily by mouth for 48 hours and then 300 mg. twice daily for the next five days. (*b*) Those who had had previous antibiotics were given 250 mg. of phenoxymethylpenicillin four-hourly by mouth for 48 hours and then 250 mg. six-hourly for the next five days and intramuscular streptomycin 0.5 g. twice daily for all seven days.

Other treatment was not standardized, but in all cases it included oxygen and antispasmodics, and in some instances also digoxin and diuretics.

A clinical and bacteriological assessment of the patients was made on admission and two days after antibiotic treatment had been stopped—that is nine days after admission—by recording the following findings:

1. Abnormal physical signs in the chest.

2. Examination of the sputum macroscopically and microscopically and bacteriological culture (see bacteriological methods below). The purulence of the sputum was graded macroscopically as follows: mucoid=grade O; mainly mucoid with purulent flecks=grade 1; mainly but not uniformly purulent=grade 2; and uniformly purulent =grade 3. In addition the volume of sputum produced by the patient in 24 hours was measured.

3. The highest temperature in the 24 hours. The mean rise in each group above 98.4° F. (36.9° C.) before and after treatment was calculated.

4. Pneumonic consolidation on a postero-anterior and lateral chest radiograph. For comparison this was graded as follows: definite consolidation=grade 2; doubtful= grade 1. If the reporting radiologist considered that consolidation was reduced in the second film the latter was classed as grade 1.

5. Total white blood cell counts (W.B.C./c.mm.).

6. Erythrocyte sedimentation rate (E.S.R.) in one hour (Westergren).

7. Mixed venous P_{CO_2} was measured by the rebreathing method of Campbell and Howell (1960), using the modified Haldane's apparatus (Campbell, 1960) to determine CO_2 content of the bag.

8. Peak expiratory flow (P.E.F.) in litres/minute was measured, using the peak flow meter described by Wright and McKerrow (1959). The lowest measurable flow was 60 l./min. Some patients who were unable to achieve this on admission exceeded it subsequently, so in calculating mean change in these circumstances a level of 60 l./min. on admission has been assumed.

In comparing the treatment groups dyspnoea (in the period before the acute exacerbation) was graded (1–5) as proposed in the Medical Research Council's (1960) questionary. On the ninth day the forced expiratory volume in one second ($F.E.V._1$) was measured on a modification (McFerrow *et al.*, 1960) of the Gaensler type of spirometer. It did not prove practicable to measure the $F.E.V._1$ through the course of the illness. Some findings were recorded on other days of the illness; but these additional results, with the exception of those of bacteriological examination of the sputum after two days of treatment, have not been used in the comparison of the groups.

Side-effects, particularly skin rashes and gastrointestinal symptoms, were inquired for specifically on several occasions during and after each course of antibiotics.

Bacteriological Methods

Gram-stained films were made from purulent areas of sputum. The remainder of the sputum was then homogenized by the addition of an equal amount of 1% pancreatin and shaken at 37° C. for one hour (Rawlings, 1953). The homogenate was diluted 10^{-2} and

10^{-4} in normal saline, and standard loopfuls of the neat homogenate and the two dilutions were transferred to blood-agar and heated blood-agar plates. Direct antibiotic sensitivity tests were performed by the ditch-plate method, the ditches containing ampicillin 50 μg./ml., chloramphenicol 50 μg./ml., streptomycin 20 μg./ml., and tetracycline 25 μg./ml., and the zone of inhibition was compared with that of an Oxford staphylococcus. Viable counts were made of the main pathogens after 18 hours' incubation. *Haemophilus* species were identified by testing for growth in the presence or absence of X and V factors, and pneumococci by sensitivity to optochin. Coliform bacilli were identified by fermentation reactions.

Results

Comparability of Groups (see Table I).—Eighteen patients were treated with ampicillin and 17 with either demethylchlortetracycline or phenoxymethylpenicillin and streptomycin. There were differences between the groups in some respects but there did not appear to be any consistent bias which could be expected to make the prognosis worse in one group than in the other; for instance, in the ampicillin group there were more patients with a raised temperature and raised white-cell count, but their ventilatory function and mixed venous P_{CO_2} were less abnormal than the group treated with other antibiotics. Twenty patients had had previous antibiotic therapy—nine in the ampicillin group and 11 in the penicillin and streptomycin group. When the two groups were subdivided into those who had and those who had not previously received antibiotics the main difference that emerged was the high age of the patients who had not received previous antibiotics. Seven of the nine in the ampicillin group and four of the six in the demethyltetracycline group were aged 70 or more.

Clinical Results

Table II gives the findings two days after a week's treatment with an antibiotic. Some findings are given as numbers of patients, and others are expressed as mean change compared with the findings on admission.

Deaths.—Three patients—a man of 70 and a woman of 73 in the ampicillin group, and a man of 82 in the penicillin and streptomycin group—who all had evidence of bronchopneumonia, died within 12 hours of admission. The fourth death occurred in a woman of 74 who on admission had a patchy bronchopneumonia: she was treated with penicillin and streptomycin with a little improvement, and a repeat chest radiograph showed resolution of the pneumonia. But she developed gross heart failure and died on the sixth day after admission. Necropsy showed acute bronchitis but no evidence of pneumonia.

Abnormal Physical Signs in Chest.—Rhonchi and moist sounds were present in the majority of patients on admission but there was little change on the ninth day.

Sputum.—Twelve of the 18 surviving patients who had had a previous course of antibiotics were still producing purulent sputum (usually grade 1) on the ninth day compared with 5 of 13 who had not had earlier antibiotics. In all groups there was a decline in the grading of the purulence of the sputum and in the volume produced in 24 hours.

Temperature.—This was still above normal on the ninth day in 9 of the surviving 31 patients—five who had received ampicillin and four who had had other antibiotics.

Chest Radiograph.—Twenty-two patients had patchy consolidation on admission. The patients treated with ampicillin who had had a previous course of antibiotics showed little improvement by the ninth day. In all, 12 patients still showed radiological evidence of consolidation at this time, six in each group.

White Blood-cell Count.—There was a larger initial rise in the count and a greater fall in the subsequent nine days in the ampicillin-treated patients.

E.S.R.—Results were very variable and abnormality was frequent at the ninth day, when 15 patients had

TABLE I.—*Comparison of Clinical Assessment on Admission*

Treatment	No.	Mean Age (Years)	70 Years or Over	Male	Female	Dyspnoea (Mean Grade*)	Heart Failure (No.)	Sputum Purulence (Mean Grade*)	Sputum 24-hr. Vol. (ml.)	Temp. Raised (No.)	Temp. (Mean Rise °F.)	Chest X-ray Consolidation (No.)	W.B.C. /c.mm.	E.S.R. (mm. in 1 hr.)	Mixed Venous P_{CO_2} (mm. Hg)	P.E.F. (l./min.)	F.E.V.$_{1}$ (l.)
Ampicillin	18	66	8	9	9	3·4	3	1·7	70	14	+1·1	10	12,100	30	55	87	0·83
Other antibiotics	17	66	7	11	6	3·2	5	1·8	72	9	+0·6	12	8,700	44	61	81	0·69

* For details of grading of dyspnoea and sputum purulence see "Methods."

TABLE II.—*Clinical Assessment on Ninth Day after Admission*

	No.	Deaths (No.)	Sputum Still Purulent (No.)	Sputum Mean Change in Purulence Grade*	Sputum 24-hr. Vol. Mean Change (ml.)	Temp. Mean Change (°F.)	Chest X-ray Still Consolidation (No.)	Chest X-ray Mean Change in Consolidation Grade*	W.B.C. Mean Change /c.mm.	E.S.R. Mean Change (mm. in 1 hr.)	Mixed Venous P_{CO_2} Mean Change (mm. Hg)	P.E.F. Mean Change (l./min.)	Further Antibiotics (No.)	Hospital Stay (Mean)
Ampicillin:														
No previous antibiotic	9	2	2	−1·0	−16	−0·8	1	−1·5	−2,400	+12	+2	+26	2	23
Previous antibiotic	9	0	7	−0·9	−40	−0·9	5	−0·3	−3,600	−12	−3	+25	8	27
Demethylchlortetracycline ..	6	0	3	−1·2	−30	−0·7	2	−1·3	−1,800	−46	−2	+6	2	21
Phenoxymethylpenicillin and streptomycin ..	11	2	5	−1·0	−26	−0·4	4	−1·2	−1,700	−1	−4	+16	3	18
Ampicillin groups	18	2	9	−0·9	−31	−0·8	6	−0·8	−3,000	0	−1	+26	10	25
Other ,,	17	2	8	−1·1	−27	−0·5	6	−1·3	−1,700	−13	−3	+12	5	19
Total ..	35	4	17	−1·0	−29	−0·7	12	−1·0	−2,400	−7	−2	+19	15	22

Mean change is between the figure on admission and on the ninth day.
* For details of grading of sputum purulence and of radiological consolidation see "Methods."

an E.S.R. of over 20 mm. in one hour compared with 18 patients on admission. Three patients in the ampicillin-treated group who had not had previous antibiotics showed a rise in E.S.R. This resulted in a mean rise in the group. But in only one patient was the rise associated with a clinically poor response.

Mixed Venous Pco_2.—Changes were small in all groups.

Peak Expiratory flow.—The mean increase was slightly greater in the patients treated with ampicillin.

Further antibiotics were given to 15 patients during the hospital admission, including 11 of the surviving 18 patients who had had antibiotic treatment preceding admission and were therefore receiving a third course. Eight out of the nine patients who were given ampicillin, having already had a previous antibiotic, later received a third course of antibiotics because of the persistence of purulent sputum and in some cases persisting radiological consolidation.

Average hospital stay was a few days longer in the ampicillin group.

Side-effects.—Despite frequent inquiry, these were recorded in only two patients, both of whom complained of epigastric discomfort, one following demethylchlortetracycline and the other after phenoxymethylpenicillin. No side-effects were encountered with ampicillin.

Bacteriological Results

H. influenzae or *Str. pneumoniae* were isolated in significant numbers from the sputum of 22 out of the 35 patients admitted to the trial; no pathogenic organisms were isolated from the remaining 13 patients, nine of whom had had previous antibiotic treatment. The number of isolations of these two pathogens from the 31 surviving patients is shown in Table III. *H. influenzae* was mainly eliminated in both treatment groups. Viable counts showed large variations, but the numbers of *H. influenzae* present in specimens 2 and 3 showed a considerable reduction in all cases. *Str. pneumoniae* was eliminated in both treatment groups but was isolated in significant numbers from the sputum of four patients two days after the end of treatment with penicillin and streptomycin. The sputum of only one of these patients showed an increase in purulence. No increase in resistance of either *H. influenzae* or *Str. pneumoniae* to ampicillin, tetracycline, or streptomycin was found after treatment.

TABLE III.—*Bacteriological Results*

Treatment	No.	*H. influenzae*				*Str. pneumoniae*			
		1	2	3	(3)	1	2	3	(3)
Ampicillin	16	6	3	1	1	4	0	0	0
Demethylchlortetracycline or penicillin and streptomycin	15	9	5	2	1	5	1	0	4

1 = Number of isolations before treatment. 2 = Number of isolations at end of 2 days' treatment. 3 = Number of isolations 2 days after stopping antibiotics. (3) = Number of isolations of organisms not previously present 2 days after stopping antibiotics.

Superinfection with coliform bacilli and Staph. aureus.—Coliform bacilli were isolated from 13 of the 16 surviving patients in the ampicillin-treated group and 9 of the 15 in the other treatment group. Most of the strains (in both groups) were ampicillin-resistant. These organisms were usually present in small numbers and occurred in mucoid as well as in persistently purulent sputum, but in one patient with bronchiectasis the isolation of a heavy growth of *Pseudomonas pyocyanea* following treatment with ampicillin was associated with an increase in purulence. *Ps. pyocyanea* was also isolated in small numbers from two other patients in the ampicillin-treated group, but in neither of these was there an increase in purulence of sputum. Before treatment was started *Staph. aureus* was isolated in small numbers from the sputum of five patients. Four of these strains were penicillin-resistant and three of the patients from whom these strains were isolated were treated with ampicillin without any great increase in numbers of staphylococci developing during treatment.

Summary of Results

The mean improvement in all groups in the sputum purulence and volume, temperature, chest radiograph, white blood cell count, and P.E.F., and the reduction in pathogenic organisms isolated from the sputum showed that all three antibiotic regimes appeared to be clinically and bacteriologically "effective." The ampicillin group were rather more ill on admission, showed less improvement in the chest radiograph, had a slightly longer average hospital stay, and more of them were given a further course of antibiotics. Persistent radiological consolidation (9 out of 13 patients) and purulent sputum (12 out of 16 patients) were frequent in patients who had had antibiotics before admission; 11 of these patients were given a third course of antibiotics.

Discussion

The results suggest that there is little to choose between ampicillin and other antibiotics in the treatment of acute exacerbations of chronic bronchitis as judged by clinical and bacteriological criteria. The changes in P.E.F. and chest radiography, also the number of patients requiring further antibiotics and the length of hospital stay, were not significantly different in the two treatment groups ($P>0.01$). The numbers we have treated would not enable us to see a relatively small benefit in the treatment of a condition which has a good spontaneous recovery rate. In both treatment groups there was a greater reduction in the number of isolations of *H. influenzae* after treatment than occurs on a placebo (Elmes *et al.*, 1957). Gastro-intestinal side-effects, especially diarrhoea and pruritus ani, have been common with tetracyclines in the past, and ampicillin may prove to be less troublesome in this respect. Ampicillin therefore appears to provide a useful addition to the range of safe and effective drugs available for treating exacerbations of infection in chronic bronchitis.

Summary

A trial of ampicillin compared with either demethylchlortetracycline or phenoxymethylpenicillin and streptomycin in the hospital treatment of infective exacerbations of chronic bronchitis was made in 35 patients. The clinical and bacteriological results suggested that ampicillin was an effective treatment, but it was not possible to show any difference between treatment with ampicillin and that with the other antibiotic regimes. No side-effects were encountered.

We thank Dr. Mary Barber and Dr. C. M. Fletcher for their advice, the consultants of the department of medicine for allowing their patients to be entered in this trial, and Mrs. S. Warren for technical assistance. We also thank Beecham Research Laboratories Ltd. for supplying the ampicillin.

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FUSIDIC ACID: LABORATORY AND CLINICAL ASSESSMENT

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Reports have recently been published on the laboratory (Godtfredsen *et al.*, 1962; Barber and Waterworth, 1962; Hilson, 1962) and preliminary clinical (Scowen and Garrod, 1962; Taylor and Bloor, 1962) attributes of fusidic acid and its sodium salt ("fucidin"). In its chemical structure, relationship to cephalosporin P (Baird *et al.*, 1961) and helvolic acid (Allinger and Coke, 1961), and in its selective antibacterial spectrum, this substance is of considerable interest. We are therefore presenting here a summary of our own assessment of fucidin in the laboratory and in the treatment of staphylococcal infections during the past two years.

Microbiological Results

Our results under this heading are largely in accordance with those previously reported (Godtfredsen, *et al.*, 1962; Barber and Waterworth, 1962; Hilson, 1962). The following points deserve separate comment:

1. Of 200 fresh clinical isolates of penicillinase-forming *Staphylococcus aureus*, all except four were inhibited in nutrient broth by 0.1–1 μg. of fucidin per ml., provided the inocula were 10^6 cells/ml. or less.

2. The minimal inhibitory concentration against staphylococci was closely dependent upon size of inoculum; large inocula (>10^6 cells/ml.) of some strains resisted the action of fucidin at 10 μg./ml.

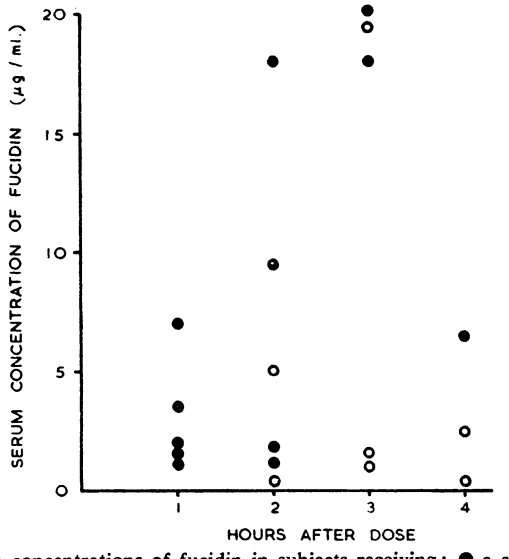
3. The effect of fucidin was bactericidal; with average inocula of most strains (10^4–10^5 cells/ml.), 30–60% of cells were killed in four hours and 80–95% in eight hours.

4. On agar flood-inoculated plates, all fresh isolates were well inhibited by disks of 1–10 μg. When heavy inocula were used, discrete colonies were present in the inhibitory zones; some of these colonies, titrated individually, were resistant to the drug at 10 μg./ml.

5. Serial passages of eight strains on agar plates containing rising gradients of fucidin produced slow acquisition of resistance during the first five days and a rapid increase thereafter, maintained on subculture in drug-free medium.

6. No destruction of fucidin was detected in 12-hour broth cultures, either of sensitive organisms growing in subinhibitory concentrations or of organisms with induced resistance growing at higher concentrations.

7. Fucidin was tested by the following methods for evidence of synergy with penicillin G against penicillinase-forming staphylococci. (*a*) Liquid cultures were prepared, incorporating each drug, separately and together in chessboard fashion, in concentrations of 0.1–20 μg./ml. By this means each concentration of each drug was tested against all concentrations of the other drug for evidence of increased (or decreased) bactericidal effect by colony counts plated at four hours; differences in bacteriostatic activity were checked by turbidity readings after overnight growth. By this means an enhanced bactericidal effect against one penicillinase-forming strain (out of nine tested) was observed with a range of concentrations of 0.05–0.2 μg. of fucidin and 0.5–5 μg. of penicillin G per ml. (*b*) Cellulose-acetate membranes (Courtaulds grade AP, 6 cm.) were placed on poured agar plates incorporating an indicator organism (Oxford staphylococcus) with an inhibitory concentration of penicillin G (2 μg./ml.). Centrifuged cells from cultures of staphylococci grown in subinhibitory concentrations of fucidin were placed on top of the membranes and incubated overnight. The membrane was then removed and the plates were incubated for a further 18–24 hours. Penicillinase formed by the organisms diffused through the membrane,



Serum concentrations of fucidin in subjects receiving: ● a single dose of 6 mg./kg.; ○ 20 mg./kg./day in three doses. Assays on nutrient agar, using *Oxford staph.* as indicator organism and known concentrations of fucidin dissolved in serum.