it most useful in assessing the severity of pulmonary involvement in diseases such as scleroderma and disseminated lupus erythematosus and the response of patients with fibrosing alveolitis to treatment.¹⁰

There is, we think, a place for much greater development of pulmonary function laboratories in general hospitals. The information obtained even with relatively simple equipment is of value to general and chest physicians, anaesthetists, and surgeons in both diagnosis and assessment. For the small capital outlay required the amount of clinically useful information which can be obtained is unparalleled by any other department.

Appendix

APPROXIMATE COST OF EQUIPMENT

	£
(1) Vitalograph dry spirometer (Instruction book includes prediction nomograms and correction tables for B.T.P.S.)	97
Stand	30
100 Charts	8
From Vitalograph Ltd., Maids Moreton House, Buckingham	
(2) Wright's peak flow meter	40
From Airmed Ltd., Edinburgh Way, Temple Fields, Harlow, Essex	
(3) Medihaler-Iso	less than 1
From Riker Laboratories, Morley Street, Loughborough, Leics	
(4) Rapid CO ₂ analyser (Hartman)	1,500
From P. K. Morgan Ltd., 10 Manor Way, Chatham, Kent	
(5) Simplified Haldane apparatus (Campbell-Howell)	27
From Aimer Products Ltd., 56 Rochester Place, London N.W.1	
(6) Resparameter mark IV	1,950
From P. K. Morgan Ltd., 10 Manor Way, Chatham, Kent	
(7) Godart Pulmotest and helium analyser	1,500
From P. K. Morgan Ltd., 10 Manor Way, Chatham, Kent	

(8) Allpyral allergen extracts (we use routinely control, mold mix, grass mix, nettle, horse epithelia, dog epithelia, house dust, house-dust mite, flower mix, <i>Cladosporium herbarum</i> , cat epithelia, feather mix, <i>Alternaria tenuis</i> , <i>Aspergillus fumigatus</i> , tree mix)	20
From Dome Allergy Unit, Stoke Poges, Slough, Bucks	
(9, 10) Blood gas and pH machines:	
BMS 3 (pH, PCO ₂ , PO ₂ electrodes with water-bath)	510
PHM 71 meter (scale)	255
PHM 72 meter (digital)	495
	765 or 1,005
BMS 2 (tonometer, water-bath, and pH electrode)	460
PHM 71 meter (scale)	255
PHM 72 meter (digital)	495
	715 or 955

From V. A. Howe Ltd., 88 Peterborough Road, London S.W.6

(11) Body plethysmograph and respiration computer	12,000
From Erich Jaeger, Wurzburg, Germany	
(12) Pneumotachograph with integrator	560
From Mercury Electronics, 64 Argyle Street, Glasgow	
(13) Paramagnetic oxygen analyser	200
From Servomex Controls Ltd., Crowborough, Sussex	

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Hospital Topics

Causes of Failure in Antibiotic Treatment*

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Accounts of therapeutics are usually a record of success, and anyone who chooses to describe only failures may be thought a pessimist or a cynic. This would be unjust; much can be learnt from failures, and they are often long and vividly remembered. Moreover, to bear in mind causes of failure should enable you to steer a course which avoids them to success.

The causes of failure may be either in the nature of the disease treated or in the choice or mode of use of the antibiotic.

* Based on a lecture given at Mount Vernon Hospital, Northwood, on 14 October 1972.

Wokingham, Berks.

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Conditions Insusceptible to Treatment

Penicillin is not a panacea for fever. To utter this truism in a country with a relatively good record for discriminating use of antibiotics almost calls for an apology, but the freedom with which they are prescribed or even self-administered in some parts of the world for trivial or inappropriate reasons is deplorable. It is on record in a famous journal¹ that a girl who had been given oral penicillin for earache (twice), for a pain in the knee, and for toothache and went into severe shock after the last dose was under the impression that penicillin is an analgesic. A seriously ill febrile patient may rightly be given an antibiotic on some explicit assumption with regard to the nature of the infection, but only after specimens have been obtained by which this can later be verified. It is a therapeutic crime to begin the treatment of a supposed bacterial endocarditis before blood cultures have been done, since it then becomes difficult to grow the organism and thus determine the proper treatment. Bacteriological diagnosis in purulent meningitis can be hampered in the same way, but in this far more urgent condition the benefit of early treatment may outweigh the drawback of not knowing its cause.

Acute febrile infections of the air passages are frequently caused by viruses, on most of which no antibiotic has any action whatever. Although recognizing this, many doctors prescribe antibiotics with the object of preventing secondary bacterial infection. There is little evidence that this is useful and it seems that patients sufficiently predisposed (in this or other ways) to secondary pneumonia will simply be attacked by an organism resistant to the antibiotic used, such as *klebsiella*, instead of a much more tractable pneumococcus which might have been responsible otherwise. Such treatment may nevertheless be justified for patients at special risk or during an influenza epidemic complicated by bacterial pneumonia.

Failure in appropriate antibiotic treatment may be due to neglect of other necessary measures. These may be surgical; naturally no chemotherapy can drain an abscess, dissolve urinary calculi, or restore a bronchiectatic lobe to normality. A form of accessory treatment which although also important is much simpler is control of urinary pH. No aminoglycoside (streptomycin, kanamycin, gentamicin) should be given for urinary tract infection until the urine has if necessary been rendered constantly alkaline, since these antibiotics are far more active in an alkaline medium. Alkalinity also enhances the activity of erythromycin, but so little of the antibiotic is excreted in the urine that recent proposals² that it be used for this purpose make little appeal, particularly since there are so many effective alternatives.

Errors in Choice of Antibiotic

In a recent review of this subject in a leading German journal³ the story is told of a doctor who prescribed Paraxin for a patient and when this had no effect changed the prescription to Leukomycin. This proved equally disappointing, which is not surprising since each of these is a brand name of chloramphenicol. The German fondness for proprietary names, which is baffling to foreign readers because they have difficulty in discovering what these mean, has thus another disadvantage. Naturally the prescriber must know what he is prescribing, and official names are generally preferable. On the other hand, there are two important antibiotics which it may be safer to prescribe by their original proprietary names. When patents on antibiotics expire less experienced manufacturers begin to produce them, and although their capsules of chloramphenicol⁴ and tetracycline⁵ contain the stated amount of antibiotic it is sometimes much less well absorbed than the original product. Some of these differences are quite large enough to make the difference between success and failure in treatment.

Failure is more certain if the antibiotic is the wrong one for the purpose. If the prescriber has to make the choice unaided, either he may be wrong in his assumption about the nature of the infection or his knowledge of what each antibiotic is capable of doing may be imperfect. Even if he knows its normal "spectrum" he may not be aware of the frequency with which normally sensitive species are resistant. Tetracycline was regarded in the past as good for almost anything, and it was originally claimed that pneumonia would respond to it whatever the microbic cause. Even pneumococci are now quite commonly resistant to it; so are haemolytic streptococci, which prejudices the treatment of sore throats, staphylococci, *Clostridium welchii*, and various Gram-negative species. A particular misconception, part of a vague belief that ampicillin is a sort of "super-penicillin" for all purposes, is that it is effective against penicillin-resistant staphylococci and thus, for instance, the antibiotic of choice for osteomyelitis.⁶ The fact is that it is just as easily destroyed by staphylococcal penicillinase as penicillin itself; what is wanted here is a penicillinase-resistant derivative such as cloxacillin.

As a bacteriologist I am ashamed to have to confess that a wrong choice may be the fault not of the prescriber but of the laboratory. A specimen is rightly sent there, something is cultivated from it, sensitivity tests are done, and treatment is based on their results and fails. There are several possible explanations for this. One is that in a mixed culture the wrong organism has

been identified as the pathogen. Sputum in particular often contains a varied flora, perhaps including more than one potential pathogen, and not only experience but some clinical knowledge may be necessary in deciding which of them matters. Secondly, the test itself may have been at fault—in method, execution, or interpretation. When a culture of *Staphylococcus aureus* is sent to 33 laboratories and 11 report it as sensitive to penicillin, 19 as resistant and, 3 as doubtful⁷ there must be something wrong. Four "quality control" surveys, two in Great Britain and two in Australia, have all given some results of this kind. There is a serious need for standardizing methods of doing these tests, and proposals to that end have recently been put forward.^{8,9} It is to be hoped that any instructions which may be issued will include a warning against doing and reporting the results of totally inappropriate tests. Reports of this kind have been known to lead to such absurdities as the treatment of pneumonia with nitrofurantoin. Sensitivity tests to this and other drugs acting only in the urinary tract should be done only with organisms from urine.

Toxicity Factor

Treatment may reasonably be said to have failed when a patient dies as a direct result of it. Chloramphenicol is the only antibiotic which when given in the normal way to apparently normal people is capable of killing them, and although estimates of the frequency with which it causes aplastic anaemia vary enormously¹⁰, the existence of the risk is undeniable. It has often been said that the only absolute indications for it are typhoid fever and *Hemophilus influenzae* meningitis. Even these are now doubtful, co-trimoxazole being an apparently effective alternative for the first¹¹ and ampicillin for the second.¹²

In general, when two antibiotics will serve the same purpose the less toxic should be preferred. Another important example of toxicity is that of aminoglycosides for the eighth nerve. There are indications for streptomycin, kanamycin, or gentamicin for which nothing else will serve equally well, and with due precautions they can safely be given. But the casual and often unnecessary administration of streptomycin with penicillin as operation cover is to be deplored, both for this and for other reasons. In patients with unrecognized impairment of renal function only a few doses can cause vestibular damage.

Outdated Forms of Antibiotics

A recent review of this subject,³ quoted above, lists among 12 types of error in prescribing the use of older forms of a drug now succeeded by better ones. This need rarely be a cause of actual failure but it should be remembered that if lincomycin appears to be indicated clindamycin (7-chloro-7-deoxylincomycin) is better absorbed and much more active against some bacteria, and if ampicillin is indicated amoxycillin, which has the same antibacterial action, is about twice as well absorbed.¹³ The newer derivatives thus appear preferable.

Administration by the Wrong Route

Only parenteral injection can guarantee full therapeutic effect, and the list of antibiotics which although they can be given by mouth may then have an inadequate effect is a long one. At the head of it is penicillin G, and it is surprising that authorities both here and in the United States still countenance its use for the prophylaxis of rheumatic fever. The results are poor¹⁴ and penicillin V, which is much better absorbed, should be preferred. Cloxacillin, ampicillin, and erythromycin are all incompletely absorbed, cloxacillin particularly if given with food, and erythromycin sometimes quite inadequately unless given as the estolate¹⁵; in the initial treatment of a severe infection it is better to administer any of them parenterally.

Wrong Dosage

This may be inadequate or excessive. Inadequacy is less often dependent on the size of the dose than on the length of the interval between doses. This is sometimes illustrated in attempts to treat outpatients with parenteral penicillin. I recollect a patient with cervicofacial actinomycosis who attended the hospital daily for an injection of (I think) one megaunit of penicillin and was apparently no better after a month; he still oozed pus full of sulphur granules. Had a quarter of this dose been given four times a day he might by then have been cured. Even procaine penicillin with its more prolonged action is better given twice a day than once for any serious purpose.

What may be regarded as excessive dosage is also most often seen in the use of penicillin. The standard dose for treating endocarditis in some hospitals, however sensitive the organism, is 20 megaunits daily, and as much as 100 megaunits has been given, although usually for infection by less sensitive bacteria. This quantity is more than double the amount which we received for all purposes *per month* at St. Bartholomew's Hospital when four of the London medical schools were first enabled to study the clinical use of penicillin in 1943. Our regular dose for a systemic infection, which it often overcame, was 15,000 units three-hourly.¹⁶ It now seems ludicrous that a gift of penicillin from this country which I took to Paris after the liberation should have consisted of only 25 million units, one-quarter of the quantity now sometimes given to a single patient in one day. At that time, so I was told, the black-market price of penicillin in France was one franc per unit; at that rate this lavish modern treatment, if supplies had been available for it, would have cost £1,000,000 a day.

Now that the genius of chemical engineers has provided limitless supplies at almost ridiculously low cost it is certainly better to err on the generous side in dosage than the other way. Nevertheless, there are at least three objections to daily doses of 20 megaunits or more unless for exceptional indications; they are wasteful, they involve a risk of producing haemolytic anaemia in a patient who has had penicillin before,¹⁷ and they may actually be less effective than a moderate dose. Penicillin is unique in that there is an optimum concentration for its bactericidal action, only about 10 times that required to inhibit growth, above which no increase will accelerate it, and for two important species, *Staph. aureus* and *Streptococcus faecalis*, the bactericidal action on most strains is actually retarded by such an increase.¹⁸ So far as penicillin-sensitive *Strep. viridans* endocarditis is concerned we are now assured by the late Morton Hamburger of Cincinnati and his colleagues¹⁹ that it will regularly respond to only 14 days' treatment with moderate oral doses of penicillin V together with injections of streptomycin.

Needless to say, excessive doses of other antibiotics increase the risk of toxic effects; an example is the renal damage which may thus be caused by polymyxins or cephaloridine.

Wrong Timing

The sooner most antibiotic treatment is started the better (although it has been argued that prompt penicillin treatment of a streptococcal sore throat inhibits a valuable defence reaction²⁰), but different considerations apply to prophylactic use. If the administration of penicillin as cover for dental extraction is begun too early the sensitive flora of the mouth is suppressed and resistant strains take its place. This led in two cases within my own experience to the establishment of an endocarditis due to highly resistant streptococci.²¹ This risk is now better recognized and the first dose of penicillin is given at such a time that the initial peak level in the blood coincides with the extraction.

Antagonistic Combinations

The advantages and drawbacks of giving two or more antibiotics together form a large subject in themselves, into most of

which I cannot enter here. I can only affirm my strong belief that there is one type of combination which should always be avoided. This consists of a bacteriostatic antibiotic (tetracycline or chloramphenicol) and a bactericidal (usually a penicillin), and the objection to it is that the bactericidal component kills only multiplying bacteria and the other prevents this multiplication. The reality of this effect is easily shown *in vitro* and has been exhaustively illustrated in therapeutic tests on animals. In one such experiment the mortality in infected mice treated with penicillin was *nil*, and when oxytetracycline was given in addition to the same dose of penicillin 60% died.²²

The antagonism of chlortetracycline and penicillin was all too convincingly illustrated in the classical study by Lepper and Dowling²³ of the treatment of pneumococcal meningitis, and has also been shown in a less disastrous way in the treatment of streptococcal sore throat.²⁴ It is for the treatment of meningitis of unknown cause that such combinations are often used in order to cover all aetiological possibilities, one commonly used being a sulphonamide, penicillin, and chloramphenicol. There is good evidence that a single bactericidal antibiotic, ampicillin, gives better results than such mixtures whichever of the three common causes of acute meningitis is responsible.¹² The objection to using antagonistic combinations for infections of other systems is less cogent but there can rarely be even an apparent need for them.

Misguided Prophylaxis in Surgery

This is a perennial subject of controversy, only one aspect of which arises here because some of the methods used undoubtedly do more harm than good. The practice of administering broad-spectrum antibiotics or combinations (such as penicillin plus streptomycin) for several days with the object of preventing wound or chest infections after operation is now discredited, although far from being universally abandoned. In controlled studies it has failed in its objects²⁵ and presents hazards of its own, including liability to staphylococcal enterocolitis, and to ototoxicity if streptomycin is used.

We must nevertheless recognize that there are operations for which some cover is desirable, because local infection may have peculiarly damaging consequences. It is worth considering what exactly this medication is designed to do, and a sensible objective is to kill any bacteria which accidentally contaminate the site of operation during its progress. If this be accepted no purpose is served by starting administration 24 hours beforehand, yet this is common practice in cardiac surgery. Bactericidal antibiotics are preferable; treatment with them started at operation should not need to be long continued. Several very large doses of penicillin,²⁶ three of cephaloridine,²⁷ and three of a mixture of penicillin, methicillin, and chloramphenicol²⁸ (which for reasons already stated might be improved on) all reduced the frequency of postoperative wound infection substantially. A single moderate dose of ampicillin failed,²⁹ but the authors of this trial did not say how many subsequent wound infections were due to penicillin-resistant staphylococci, on which ampicillin has little action.

This subject provides an opportunity, for which I am grateful, of expressing strongly held views, some first developed many years ago, on how antibiotics should and should not be used. They are personal views, and anyone is entitled to disagree with them if he has grounds for doing so. I trust that he will not find any fault with the facts presented or cause for offence in any deductions made from them.

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Clinical Problems

Organization of Clinical Trial on National Scale: Management of Early Cancer of the Breast

M. BAUM, M. H. EDWARDS, C. J. MAGAREY

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Summary

From a study of the organization of a national clinical trial on the management of early cancer of the breast in women there appear to be overwhelming advantages in studying large numbers of patients. To this end centres abroad have been encouraged to join. All the evidence at present suggests that it is feasible to organize a study on this scale, that the documentation and follow-up are accurate, and that the enthusiasm of the participants can be successfully fostered and maintained.

Introduction

There can be no doubt about the magnitude of the problem of the management of early cancer of the breast. It is the commonest malignant disease in women in the United Kingdom; one in 17 develops the disease and over 10,000 die from it each year.¹ Despite all our efforts over the past few decades there is little information about which of the different forms of present-day therapy alters the course of the disease for the good of the patient, which has little or no effect, and which may even be harmful. Experience points to the fact that only prospective, randomized clinical trials involving many patients are likely to provide firm facts on which rational decisions can be based. Few such clinical trials have been carried out.²⁻⁶ All treatment methods compared were based on the traditional view of tumour spread,⁷ where it is assumed that malignant cells in

the breast or regional nodes must be either surgically removed or "sterilized" by radiotherapy.⁸ Thus all methods compared showed a final common pathway of "radical" intent.

In 1969 over 100 clinicians, representing most of the regions in the United Kingdom, met at Cambridge to discuss the management of early cancer of the breast. The outstanding feature was the doubt and uncertainty about the best form of treatment. A survey was then carried out on the management of early cancer of the breast in almost all the regions throughout the United Kingdom. As a direct result of these promptings and inquiries an investigation was launched to study two competing forms of therapy based on conflicting concepts of the biological behaviour of breast tumours.⁸ Our survey indicated that the commonest form of radical therapy practised today is simple mastectomy with post operative radiotherapy. The Association of Surgeons confirmed that more clinicians adopted this form of treatment than any other.⁹ In addition it appears to be as successful as other forms of radical therapy.³ For these reasons simple mastectomy and radiotherapy was chosen as best representing the traditional approach. There were strong arguments that simple mastectomy alone would best represent the "conservative" attitude.

There is increasing evidence that defence mechanisms, possibly involving the regional lymph nodes and the lympho reticular system as a whole, may play a part in the tumour-host relationship.¹⁰ The radiotherapy regimens usually employed in the treatment of breast cancer depress not only local immune reactions¹¹ but lymphoreticular activity throughout the body.^{12 13} Indeed in some people radiotherapy may result in the early appearance of distant metastases.¹⁴ Our survey of the regions indicated that simple mastectomy alone would be acceptable to most clinicians. In this group a "watch policy" was adopted. If lymph nodes required treatment at a later date this would be carried out.

On further exploration of the problem there appeared to be overwhelming advantages in admitting large numbers of patients to the trial. The reasons are discussed below. This inevitably led to the idea of a trial on a national scale. After two years

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