MEDICAL PRACTICE

*Occasional Survey***Chemoprophylaxis***

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The speaker on a controversial subject enjoys an agreeable freedom; when so many views prevail he cannot agree with all of them, but he is almost certain to be applauded by someone. No one will contest that chemoprophylaxis is a controversial subject; the nearest approach to agreement is in the view that antibiotic prophylaxis is overdone. In 1955 Jawetz¹ claimed that "only 1-5% of all antimicrobial drugs are administered on proper clinical indication," and that one of the three ways in which the rest are "wasted" is for "unreasonable and largely hypothetical 'prophylaxis' of bacterial infections." Perhaps a bacteriologist is not entitled to strong views on so clinical a subject, but those that I shall express are at least soundly based in theory.

Medical uses

Chemoprophylaxis is most likely to succeed if (a) it is aimed at preventing infection by a single bacterial species, (b) this organism is fully sensitive to the drug used and will remain so indefinitely, and (c) the drug used rarely has side effects. These conditions are best fulfilled in the prevention of rheumatic fever.

RHEUMATIC FEVER PROPHYLAXIS

Attacks of rheumatic fever follow only infections with *Streptococcus pyogenes*. Sulphonamides, first used to prevent

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rheumatic fever, failed in time to fulfil the second clause of condition b; the use of sulphadiazine on a massive scale in the United States Armed Forces led to the appearance and spread of sulphonamide-resistant streptococci.² Similar use of this drug was later to breed a resistant race of meningococci,³ with the consequence that minocycline and even rifampicin have since been used for the treatment of carriers. But streptococci are incapable of becoming resistant to penicillin, so penicillin is now widely used for prophylaxis, and it is worth inquiring how it may best be administered.

It is indisputable from such studies as those in table I⁴ that a monthly injection of benzathine penicillin has by far the most certain effect—certain particularly because what the Americans call "fidelity of prophylaxis" or "penicillin compliance" is not required. Many patients who feel perfectly well cannot be depended on to take tablets regularly for months or even years.

TABLE I—Results of rheumatic fever prophylaxis⁴

Drug	Dose	Frequency per 100 patient years of:	
		Streptococcal infections	Rheumatic fever recurrences
Sulphadiazine	1 g/day	24	2.8
Penicillin G (oral)	200 000 U once daily	20.7	5.5
Benzathine penicillin	1 200 000 U once monthly	6.1	0.4

But if oral medication is preferred by either doctor or patient what form should it take? The American Heart Association prescribes a single daily oral dose of penicillin G (table I). Clearly its effect is inferior; indeed another American study,⁵ although not so interpreted by its authors, can be taken to mean that it has no effect at all. It would be surprising if it had much effect because penicillin G is poorly and irregularly absorbed, and a single daily dose exerts any effect for only a short fraction of the period it is intended to cover. Such medication is rarely if ever relied on for any other purpose. The much better alterna-

tive of using an acid-resistant penicillin, either penicillin V or one of the other phenoxypenicillins which are even better absorbed, and in two doses a day was proposed by the Ministry of Health in 1965,⁶ but with no expression of preference for either. Theoretical expectation is that an acid-resistant penicillin would have a far more certain effect, but surprisingly there is no report of a comparison of the two treatments by which this may be verified.

PREVENTION OF BACTERIAL ENDOCARDITIS

Another danger that rheumatic patients and some others face is that of developing bacterial endocarditis after operations, such as dental extraction, that cause a transient bacteraemia. These bacteria, most often salivary streptococci, may lodge in some irregularity in the endocardial surface, usually on a valve. The object of chemoprophylaxis here is to kill these bacteria before they can multiply and establish themselves. Merely bacteriostatic antibiotics such as tetracycline are useless; in these circumstances streptococci survive treatment with tetracycline for a week.⁷ The antibiotic must be bactericidal, and penicillin is the usual choice; it causes a high mortality in a susceptible bacterial population within four hours. If it can be given so that only one dose is necessary so much the better. A second important principle is that the treatment should be given only shortly before the extraction. Some seem to think that the mouth can be more or less sterilised by previous medication, but penicillin treatment can select a resistant oral flora within as short a time as two days,⁸ and in one case several days' treatment with penicillin before a multiple extraction was promptly followed by an endocarditis due to a streptococcus 400 times more resistant to penicillin than one that had caused a previous attack.

A recent inquiry by Durack⁹ among dentists showed that their practice in these patients often conforms to neither principle, and is indeed almost always inadequate if Durack and Petersdorf's¹⁰ experimental findings are correct. They damaged rabbit heart valves by means of an indwelling catheter, infected them with *Str viridans* by intravenous injection, and treated them with various antibiotics, looking for sterilisation of the valve within 24 hours. Only bactericidal antibiotics achieved this, and not all of them. A large dose of procaine penicillin succeeded, but the alternatives actually recommended by Durack⁹ are vancomycin or a large dose of penicillin together with streptomycin. Neither of these treatments will universally commend itself, and those who have hitherto been content with a single full dose of fortified procaine penicillin (BP) may be encouraged to remain so,* especially since in these experiments previous trauma produced vegetations, which may have been more difficult to sterilise than a valve not so damaged.

OTHER MEDICAL USES

Most alleged medical indications for chemoprophylaxis are beset by much greater difficulties. Chief among these is the fact that a wide variety of bacteria are capable of causing the infections which the prophylaxis is aimed at preventing. When these are of many different genera no single antibiotic can protect against them, and even a combination will leave loopholes. Moreover, resistant strains of some of these bacteria exist which will not be affected. If there is a strong predisposition to infection it is likely to develop in any case, and the only effect of antibiotic prophylaxis will be to ensure that the pathogen emerging will be resistant and the condition consequently far more difficult to treat than if nature had been left to take its course.

*Recently Fleming³⁰ has queried the feasibility of intramuscular injections in dental practice, and referred to unpublished experimental studies suggesting that a large oral dose of penicillin V may be an effective substitute; 2 g one hour before extraction followed by 0.5 g six-hourly for three days is suggested.

This consideration applies to some extent to each of the following types of infections.

Lower respiratory tract infections—Bronchitis and bronchopneumonia are complications to be feared in a variety of circumstances: after operations, particularly abdominal ones; in elderly patients; in some comatose and paralytic states; and in acute, primarily virus, infections such as influenza and measles. Many different bacteria may cause such infections, which provide one of the clearest examples of a condition in which prophylaxis may serve only to select a resistant pathogen. Thus an untreated patient's infection is likely to be pneumococcal; in the treated it may be due to a highly resistant klebsiella. Is it not better to take the chance of an infection readily amenable to treatment than to run the risk of one which is not? Among virus infections influenza may be an exception in a severe epidemic complicated by bacterial bronchopneumonia. The prevalent cause of this—often a staphylococcus in recent times—should be known, and an appropriate antibiotic (such as cloxacillin for staphylococci) may be given as a preventive measure.

Neonatal infections—Premature infants and those born in unfavourable circumstances—for example, after premature rupture of the membranes—are susceptible to infection by a variety of bacteria, and combinations of two or three antibiotics have been used in trying to prevent this. There is a strong case for withholding such treatment until some signs of infection appear. Although bacteriological diagnosis in the infant is difficult it may later become possible to choose a single appropriate antibiotic in place of a "shotgun" mixture. Amiel-Tison and Dandres¹¹ compared two groups of such infants; 83% of one group had received prophylactic antibiotics administered almost routinely, while only 23% of the other group received prophylaxis and then only for positive indications. The incidence of infections was about the same, but those in the latter group were usually due to sensitive bacteria and easily treated, while those in the former group were largely due to resistant Gram-negative species. Prophylaxis is possible at an earlier stage in premature rupture of the membranes, since ampicillin or cephaloridine given to the mother attains useful concentrations in the amniotic fluid.

Neutropenia—Severe neutropenia or agranulocytosis, however caused, renders the patient almost defenceless against attack by any potential pathogen, which will usually come from the mouth or bowel. Leukaemia under treatment with antimetabolic drugs may present this problem in its severest form. Here again there is a choice between pure prophylaxis and treatment only when signs of actual infection appear. The regimen used at the Royal Postgraduate Medical School,¹² consisting of polymyxin or carbenicillin, cephalothin, gentamicin, and clindamycin, has been misquoted as prophylactic; in most cases these antibiotics are given only on definite indications, notably fever "in the absence of obvious non-bacterial causes." Pure prophylaxis with co-trimoxazole has, however, been successful in small series of such cases.^{13 14}

Urinary tract infections—In a patient subject to recurrent attacks a small dose of sulphonamide may prevent them, taking advantage of the fact that the sulphonamides are much more effective against small numbers of bacteria, such as must initiate the infection, than against large populations. Co-trimoxazole has also been successfully used in this way for long periods, the dose sometimes being eventually reduced to one tablet every two or even three days.¹⁵ Another problem is the prevention of infection during indwelling catheterisation. If the period is limited this is perfectly feasible. Two studies in the gynaecological wards of my own hospital illustrate this; the patients were women undergoing vaginal repair operations, after which the bladder was drained for seven days. In the first study¹⁶ treatment during this period was 1 g Sulphatriad (sulphadiazine 370 mg, sulphamerazine 260 mg, and sulphathiazole 370 mg) three times a day, in the second¹⁷ 100 mg nitrofurantoin four times a day. The Sulphatriad-treated patients fared little better than untreated controls, only 15% escaping infection; in the controls most infections were due to *Escherichia coli* and other coliforms but an even larger majority of the treated patients were infected with *Strep faecalis*, a totally sulphonamide-resistant organism. In the nitrofurantoin-treated group 90% of patients escaped infection, and no infection was due to either of these organisms (table II). It is thus necessary to use a drug or combination of drugs effective against both coliforms and streptococci. An example of such a combination is sulphadiazine and penicillin, shown nearly 30 years ago¹⁸ to be capable of preventing post-prostatectomy infection.

Intestinal infections—That from which protection is most often sought by medication is "travellers' diarrhoea." Some evidence favours combinations of sulphonamides and an aminoglycoside such as streptomycin. Theoretically it seems advisable that an oral dose of such a preparation should accompany every meal, and this should not be unduly burdensome for an intelligent person during a short period

at risk. When a dose is given no more than twice a day, as in some trials of different remedies, long segments of the bowel must be left almost entirely drug-free and its pathogenic inhabitants at liberty to attack and colonise the mucosa. During known exposure to enteric fever or bacillary dysentery similar treatment would also seem reasonable, although hygienic measures must come first. Adequate prophylaxis with tetracycline can prevent cholera.¹⁹

TABLE II—Prevention of urinary tract infection during temporary indwelling catheterisation

	Sulphatriad 1 g 3 times a day		Nitrofurantoin 100 mg 4 times a day	
	Treated	Controls	Treated	Controls
Total cases	60	42	41	38
No infection	9 (15%)	3 (7%)	37 (90%)	6 (16%)
<i>E. coli</i> , etc*	6	22		27
<i>Strep. faecalis</i>	36	12		5
<i>E. coli</i> and <i>Strep. faecalis</i>	2	2		
Other bacteria	7	3	4	

*Including six *Proteus* in nitrofurantoin controls; not specified in Sulphatriad cases.

Surgical uses

In surgical practice, at least in some countries, most antibiotic treatment is prophylactic. According to Altemeier *et al*²⁰ a "spot check" of their surgical services in Cincinnati showed that 54% of all patients were receiving antibiotics, 40% prophylactically and only 14% for the treatment of established infection. The possible indications are varied.

PREVENTION OF GAS GANGRENE

True gas gangrene, or clostridial myositis, the most acute and dangerous of all wound infections, is commonly the result of gross trauma, such as battle or accident wounds contaminated with soil or dirt. The two conditions required for its establishment are the presence of spores of pathogenic clostridia, usually *Clostridium welchii*, and a low oxygen tension such as exists in muscle that has been crushed or cut off from its blood supply. Even now it does not seem to be universally understood that both of these conditions are fulfilled in amputation through the thigh for obliterating arterial disease. For a surprising distance from the anus the skin harbours *Cl. welchii* spores from the bowel, which in this operation may contaminate large areas of severed muscle, and the low oxygen tension is ensured by the disease for which the operation is undertaken. I have myself seen this operation followed by gas gangrene in two patients. Parker,²¹ in an inquiry about postoperative gas gangrene in Great Britain, obtained particulars of 56 cases (31 deaths): 39 were leg amputations, almost all for arterial insufficiency, and 11 followed other operations in this area, mainly on the hip. I would draw particular attention to his statement, "No patient who subsequently developed clostridial sepsis was being treated with adequate doses of penicillin on the day of the operation." These patients need to be given full doses of penicillin, such as 500 000 units every six hours for several, preferably five, days, and the first dose should be given at the beginning of the operation. Needless to say, gross contaminated trauma also demands this as well as surgical treatment.

BOWEL PREPARATION BEFORE COLONIC SURGERY

By administering unabsorbed or poorly absorbed antibacterial drugs the numbers of bacteria in the colonic contents can be greatly reduced, thus presumably mitigating the effects of peritoneal contamination. Gaseous distension is also reduced. Needless to say, mechanical cleansing of the bowel is equally if not more important. Not more than two days' administration of these drugs is necessary. In one trial²² neomycin, bacitracin,

and nystatin were given, and quantitative culture of the faeces showed that these produced a steep fall in the numbers of the principal bowel species, and the rate of postoperative infection was substantially reduced. A commonly used combination is phthalylsulphathiazole and neomycin. Erythromycin, which in forms other than the estolate is far from fully absorbed, is sometimes included for its effect on bacteroides. Metronidazole has also been given with the same object.

The surgical attitude that this kind of treatment is unnecessary if mechanical cleansing has been thorough is understandable, but I cannot accept the objection, voiced recently in the United States, that treatment is likely to be followed by staphylococcal enterocolitis. Azar and Drapanas²³ gave their patients neomycin and phthalylsulphathiazole preoperatively, which was followed by a 14% incidence of staphylococcal enterocolitis, but this study was vitiated by their postoperative treatment with systemic antibiotics, including tetracycline and penicillin plus streptomycin, which are well known to predispose to this infection. Staphylococcal infection can be guarded against, if necessary by including an appropriate antibiotic in the preoperative mixture, either bacitracin²² or vancomycin. This may be "shotgun" treatment, but that is no objection when the route is innocuous and the period brief.

PREVENTION OF OPERATIVE WOUND INFECTION

The prevention of operative wound infection is a highly debatable subject, complicated by the great variety of operations to be considered and the different degrees of risk of sepsis. At one time some surgeons considered antibiotic cover obligatory for almost all major surgery to prevent either wound infection or postoperative pulmonary complications, or both. This cover often consisted of about five days' treatment with a tetracycline or a combination of penicillin and streptomycin. Not only did patients so treated sometimes fare less well than controls,²⁴ but either regimen was likely to be complicated by staphylococcal enterocolitis. Moreover, only a few doses of streptomycin may be ototoxic in patients with unrecognised impairment of renal function. In Britain at least these proceedings are now largely discredited.

In most forms of clean surgery no antibiotic cover is necessary. On the other hand, cover may be advisable if the consequences of chance contamination may be disastrous, as in open heart surgery or the insertion of a hip prosthesis, or if some contamination from within is inevitable, as in many operations on the gall bladder, stomach, or bowel. These are only examples; the variety of circumstances in which susceptibility to infection has to be considered is almost endless.

Given that the object is to kill bacteria implanted in the wound at the time of operation, a few doses of a suitable bactericidal antibiotic ought to be able to achieve this, and there is now solid evidence that they can. Brief particulars of five studies mainly in patients undergoing abdominal surgery are given in table III. The practice of giving three doses, one immediately before, one during, and a third a few hours after operation was originated by Bernard and Cole,²⁵ who reduced the infection rate from 25% to 5% with a mixture of three anti-

TABLE III—Antibiotic prophylaxis of surgical wound infections around time of operation only

Year	Authors	Antibiotics and doses	No of doses	Infection rates (%)	
				Treated	Controls
1964	Bernard and Cole	Penicillin 600 000 U, methicillin 1 g, chloramphenicol 200 mg	3	5	25
1965	Campbell	Penicillin 10 MU	≥2	2	10
1969	Polk and Lopez-Mayer	Cephaloridine 1 g	3	6	29
1973	Evans and Pollock	Cephaloridine 1 g	3	9.1	14.7
1974	Stokes <i>et al</i>	Lincomycin 600 mg, gentamicin 80 mg (or tobramycin)	2	1	8

biotics. Polk and Lopez-Mayer²⁵ gave cephaloridine alone in the same way, and their practice was followed by Evans and Pollock.²⁷ Campbell²⁸ relied on large doses of penicillin alone, and Stokes *et al*⁹ reported encouraging preliminary results from two doses of a combination of lincomycin with either gentamicin or tobramycin. This form of prophylaxis is logical, innocuous, since side effects are unlikely from so few doses, and evidently effective. And it has wide applications: the more specialised uses of antibiotics in surgery, notably the prevention of infection in burns, cannot be discussed here.

Among other applications in surgery are the prevention of urinary tract infections, referred to above, and the local application of antibiotics in wounds. This is another relatively innocuous use which is to be recommended in so far as it is proved effective. This type of use and the systemic administration of only a few doses are much to be preferred to the indiscriminate and damaging systemic treatment continued for days which was in vogue 20 years ago.

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Hospital Topics

Management of uraemic pericarditis

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Summary

Of 250 patients undergoing haemodialysis from 1967 to 1974 17 presented with uraemic pericarditis. Seven of these patients who had been transferred early enough to peritoneal dialysis treatment were cured without pericardiectomy (mean survival 18 months (range 6-36); no deaths). Only one patient was cured from his pericarditis by "aggressive haemodialysis." In seven out of 10 patients treated with haemodialysis, pericardiectomy finally had to be performed because of pericardial tamponade (postoperative survival 20 months (range 8-36); one death). Two patients died from pericardial tamponade before surgery.

In patients with evidence of uraemic pericarditis

frequent peritoneal dialysis with high fluid withdrawal is the treatment of choice, but in cardiac tamponade pericardiectomy should follow a preoperative pericardiocentesis with limited fluid aspiration.

Of possible significance in the aetiology of pericarditis were the findings that 10 of the 17 patients had hypertension with cardiac enlargement and that 14 presented with evidence of underdialysis, possibly due to the reuse of dialysis components.

Introduction

The first report on pericarditis in patients with kidney disease dates back to 1836: Bright¹ observed pericarditis together with pleural and peritoneal effusion in 100 necropsy cases "connected with albuminous urine." The high frequency of pericarditis in uraemia may be shown by necropsy findings from the period before the introduction of dialysis treatment. Various workers^{7 10 14 16} observed uraemic pericarditis in 20-50% of the patients who died from uraemia.

The frequency of uraemic pericarditis has been reduced to less than 15% by the introduction of dialysis.^{4 13 17} A statistical investigation by the European Dialysis and Transplant Association, which registered 3800 deaths among patients on haemo-

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