MEDICAL PRACTICE

Occasional Survey

Choice among Penicillins and Cephalosporins*

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In 1944 medical personnel in London was scattered and communications were difficult, but a meeting at the Royal Society of Medicine in November of that year was one of the most crowded ever held there. Such an audience could then have been attracted by only one subject, penicillin, which at that time was proving its worth in the treatment of battle casualties. Of the opening speakers, Fleming is fully reported in the *Proceedings*, but Florey¹ much more briefly, and without reference to a prediction he made—namely, that “some day chemists will manipulate the penicillin molecule to improve its performance.” Fulfilment of this prophecy came 15 years later with the isolation of the penicillin nucleus, 6-aminopenicillanic acid. Until then about 30 natural penicillins had been known, whose formation could be induced by adding the appropriate precursor to the culture medium. But the only functioning precursors were derivatives of acetic acid. Removal of the side chain enabled others of quite different nature to be attached and by such means several thousand new penicillins were eventually produced.

Later the process of synthetic modification was applied to 7-aminocephalosporanic acid, the nucleus of cephalosporin C. The result of these efforts is that many penicillins and cephalosporins are now available for clinical use. It is difficult for the clinician to distinguish between the particular merits of so many similar antibiotics or to recognize the purposes for which some of them may fail, and it is the object of the following analysis to make these tasks easier. The list of those considered cannot

be exhaustive, and is confined mainly to those now available in this country. It will be necessary to go over some old ground, and indeed to summarize developments which have occupied a further 15 years since Florey's original prophecy.

The Acid-resistant Phenoxy Penicillins

One of the defects of the original penicillin (benzyl penicillin or penicillin G) was acid lability, causing most of a swallowed dose to be destroyed in the stomach. Not only is the proportion absorbed less than one-fifth, but often much less, and indeed so variable that oral therapy is undependable. The first acid-resistant penicillin was a natural product, described as long ago as 1948,² but its acid resistance then went unrecognized. It was rediscovered accidentally in a small penicillin production plant in Tyrol in 1953, where an astute plant manager noticed that the usual loss of activity had not occurred during the acid stage of extraction, and inquired into the reason for it. What he had got was phenoxymethyl penicillin, or penicillin V. This came into clinical use several years before semi-synthetic penicillins began to be produced. It is regularly but not fully absorbed, only about 25% of the dose being excreted in the urine.

Better absorption was a virtue claimed for the semi-synthetic phenoxy penicillins, phenethicillin, propicillin, and phenbenicillin, when they came into use. This, however, is only one of three properties on which the merits of such a drug depend, the others being degree of antibacterial activity and extent of protein-binding. All these were taken into account in the classical study of Bond, Lightbown, Barber, and Waterworth,³ the results of which are summarized in table I. Phenbenicillin is the best absorbed of the four, but is so heavily protein-bound as more than to negate this advantage; its manufacture has been discontinued. The last column of the table, giving the factors by which the concentration of *free* antibiotic in the blood exceeds that required to inhibit bacterial growth, shows penicillin V to be the most active against streptococci and phenethicillin against staphylococci.

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TABLE I—Comparison of Four Phenoxypenicillins³

Compound	Blood Levels at 1 hour after 250-mg dose (μg/ml)		Protein-binding (%)	Factor of Antibacterial Activity* v.	
	Total	Free		Staph.	Strep.
Penicillin V	2.27	0.36	81.8	6.0	24.0
Phenethicillin	3.57	0.64	76.4	10.7	21.3
Propicillin	3.58	0.28	89.5	2.3	9.3
Phenbenicillin	5.60	0.14	97.2	0.56	4.7

*Concentration free in blood/M.I.C.

It was often assumed that phenoxypenicillins had the same antibacterial activity as penicillin G, differing only in pharmacokinetic behaviour. This is very far from being true. There are only small differences in the sensitivity of staphylococci and streptococci, but in all Gram-negative species these differences are wide. Some personal findings⁴ on this are given in simplified form in table II. It should be clear from these that phenoxypenicillins (and methicillin) are markedly inferior to penicillin G for any Gram-negative infection; for some of these they are still more inferior to ampicillin. This serious defect has often been ignored. During a panel discussion⁵ at a conference in the United States, when poor results in gonorrhoea were reported, no one suggested that they might be due to inadequate activity of the antibiotic itself. In two comparative trials^{6, 7} of drugs for the treatment of chronic bronchitis penicillin V was one of those used; insofar as *Haemophilus influenzae* was responsible for these infections this treatment would seem to have little prospect of success. Quite recently penicillin V has again been considered seriously for the treatment of *Escherichia coli* and *Proteus* infections of the urinary tract.⁸

Phenoxypenicillins afford a convenient means of treating streptococcal and pneumococcal infections. Though they are sometimes regarded as suitable only for less severe infections, it should also be remembered that only two weeks' treatment with penicillin V combined with streptomycin has been found fully effective in *Streptococcus viridans* endocarditis when the strain is penicillin-sensitive.⁹

TABLE II—Relative Activities in vitro of four Penicillins against nine Bacterial Species

	Penicillin G	Penicillin V	Phenethicillin	Methicillin
<i>Staph. aureus</i> (pen.-sens.)	1	1	1	64
<i>Strep. pyogenes</i>	1	2	4	16
<i>Strep. pneumoniae</i>	1	2	4	16
<i>Strep. faecalis</i>	1	2	2	16
<i>N. gonorrhoeae</i>	1	8	8	
<i>H. influenzae</i>	1	8	8	8
<i>E. coli</i>	1	4	8	>8
<i>Pr. mirabilis</i>	1	32	128	64
<i>S. typhi</i>	1	64	128	256

1 = maximum activity
Other figures are the factors by which minimum inhibitory concentrations exceed this
(Data from Garrod⁴)

Penicillinase-resistant Penicillins

The next achievement was to produce derivatives resistant to the destructive action of staphylococcal penicillinase, and thus effective in penicillin-resistant infections, which were posing a serious problem, with strains also resistant to many other antibiotics as well. The first of these was methicillin, which has to be injected, but can be given in large enough doses to attain the rather high concentrations required to attack staphylococci, and has an advantage in being only 40% protein-bound. This was followed by the isoxazole penicillins, which combine resistance to penicillinase with resistance to acid, so that they can be given orally, and are more active in vitro than methicillin, but on the other hand are much more heavily protein-bound.

Among these oxacillin was at first exclusively used in the United States and cloxacillin in Britain. More recently dicloxacillin and flucloxacillin have been introduced in the two countries respectively. The relative merits of these four derivatives need to be assessed on the same lines as those of the phenoxypenicillins—factors to be taken into account (apart from intrinsic antibacterial activity, which varies little)—being efficiency of absorption and extent of protein-binding. Dicloxacillin is the best absorbed but also the most protein-bound. Table III embodies findings in the original description of flucloxacillin,¹⁰ showing that it combines good absorption with a lower degree of protein-binding, and may thus be judged on theoretical grounds to be, dose for dose, the most therapeutically efficient of the four.

TABLE III—Isoxazole Penicillins

Compound	M.I.C. for <i>Staph. aureus</i> (μg/ml)	Per cent. bound	Per cent. free	Peak Blood Level after 250mg 500mg (μg/ml)
Oxacillin	0.15	93.1	6.9	4.9
Cloxacillin	0.21	94.0	6.0	9.2
Dicloxacillin	0.17	96.9	3.1	9.3
Flucloxacillin	0.16	94.7	5.3	8.8 14.5

i.e., blood level ratios (approx)
Total Free Ox Clox Diclox Fluclox
1 1 2 2 4
(Sutherland, R., Croydon, E. A. P., and Rolinson, G. N.¹⁰)

Since these penicillins came into use the gravity of the menace from antibiotic-resistant staphylococcal infection has much diminished.

Broad-spectrum Penicillins

Another defect of penicillin G is its low degree of activity against most Gram-negative organisms except gonococci and meningococci. This too has to some extent been overcome. Not only are there two main new penicillins with considerable anti-Gram-negative activity, but these in their turn have been further modified to improve their performance.

AMPICILLIN

This derivative represented a great advance, and it is much the most widely used of all the semi-synthetic penicillins. Its action is similar to that of penicillin G on Gram-positive organisms (the similarity including susceptibility to staphylococcal penicillinase) but considerably greater against many gram-negatives, including *Haemophilus* spp., *E. coli*, *Pr. mirabilis*, *Salmonella* and *Shigella* spp. Moreover, it is acid-resistant and can thus be given orally. Small wonder that it has been so widely used for a variety of urinary and respiratory infections; among less frequent uses are for intestinal infections and meningitis. Gonorrhoea has also been treated; its action on most gonococci equals that of penicillin, but fully penicillin-sensitive strains are rather less sensitive to it and resistant strains rather more so.¹¹

Though acid-resistant, an oral dose is not completely absorbed (parenteral treatment is preferable or even essential for some purposes), and this is the defect against which further modification has been aimed; two further derivatives have resulted.

Pivampicillin

Pivampicillin is an ester of ampicillin which is much better absorbed, and after absorption is rapidly broken down with the liberation of ampicillin—which then attains blood levels fully twice those given by the unchanged antibiotic.¹²

Amoxycillin

Amoxycillin is a derivative of ampicillin which again is twice as well absorbed, but undergoes no change thereafter, and itself possesses antibacterial activity differing little from that of ampicillin.¹³

Either of these derivatives may be expected, dose for dose, to exert a more potent therapeutic effect than ampicillin itself. Amoxycillin has apparently a further advantage in greater therapeutic activity, at least in experimental *E. coli* and *Pr. mirabilis* infections, when administered parenterally.¹⁴ A possible clue to this is that, though the inhibitory activity in vitro of the antibiotics was indistinguishable, the bactericidal action of amoxycillin on these two organisms was the more rapid.

CARBENICILLIN

This derivative is distinguished by an action on *Ps. aeruginosa* much exceeding that of other penicillins, though the concentration required to inhibit growth (usually about 50 µg/ml) is high. *E. coli* and all species of *Proteus* (except β-lactamase-forming *Pr. mirabilis*) are much more sensitive. Action on Gram-positive organisms is decidedly weaker than that of ampicillin. It must be administered parenterally. Moderate doses suffice for urinary infection, but very large doses, of the order of 20-30 g daily, are indicated in a *Pseudomonas* septicaemia and may need to be reinforced both with probenecid and by also giving gentamicin.

OTHER COMPOUNDS

Ticarcillin, formerly known as BRL 2288, closely resembles carbenicillin and is used in the same way.¹⁵ Its merit is that *Ps. aeruginosa* is about twice as sensitive to it as to carbenicillin.

Indanyl carbenicillin is an ester administered orally which liberates carbenicillin after absorption. Gastrointestinal intolerance limits dosage, and the blood level attainable (about 10 µg/ml) is inadequate for systemic infection.¹⁶ This drug therefore seems to be indicated only for the outpatient treatment of urinary infections due to *Ps. aeruginosa* or the less common species of *Proteus*.

Cephalosporins

The history of these antibiotics is long and strange. *Cephalosporium acremonium* is a mould cultivated in 1945 from a sewage outfall in the area in Sardinia by Brotzu, who used crude extracts of cultures for treating typhoid fever and brucellosis. When Florey heard of it in 1948 and a culture reached Oxford it was found to produce several antibiotics, including cephalosporin N, a penicillin, and cephalosporin P, a steroid allied to the later discovered fusidic acid. A third quite different component, cephalosporin C, formed in very small amount, was not even detected until 1953. The Oxford workers obtained enough of it to show, *inter alia*, that it was resistant to staphylococcal penicillinase; no penicillin with this property was then known. More years were to elapse before the mould could be induced to give an adequate yield of it, and the study of synthetic derivatives could begin. In all, nearly 20 years passed from the discovery of the mould before these products came into clinical use.

All of them share the following advantages:

(1) An activity comparable to that of penicillin against streptococci, pneumococci, and staphylococci, these including penicillin-resistant strains.

(2) The susceptibility of various enterobacteria, including not only *E. coli*, *Pr. mirabilis*, and *Salmonella* and *Shigella* spp., but two which are resistant to penicillins, β-lactamase forming strains of *Pr. mirabilis* and *Klebsiella aerogenes*.

(3) The fact that they can usually be given safely to patients sensitized to penicillin.

For some years only two of these products were available, both of which had to be administered by injection.

CEPHALOTHIN AND CEPHALORIDINE

Cephalothin and cephaloridine were first adopted for clinical use in the United States and Great Britain respectively, but both now are available in each country. Their properties are compared in table IV. The advantages of cephaloridine are rather higher and more sustained blood levels and a lower degree of protein-binding. Its disadvantages are a lesser resistance to staphylococcal penicillinase, so that it may be ineffective in infection by a strain producing a large amount of this enzyme, and nephrotoxicity when large doses are given—particularly in patients with otherwise impaired renal function. Consideration of these factors should enable a choice between the two products to be made.

Since these cephalosporins have to be given by injection and at least four times a day, they are practically restricted to hospital use, and are in general prescribed for serious infections and on a basis of laboratory findings. Such restriction may not be a bad thing. At least it is certain that to introduce for the first time an orally administrable form of a major antibiotic will open the door to much more widespread and generally less discriminating use. However the consequences may be judged, this door is now open.

TABLE IV—Cephalothin and Cephaloridine Compared

Property	Cephalothin	Cephaloridine
Antibacterial activity	Equal v. most species	rather higher v. staph., strep., and pneumococci
Resistance to staphylococcal penicillinase	high	lower
Injection	May be painful	less painful
Protein-binding	65%	20%
Renal excretion	tubular	glomerular
Nephrotoxicity	0	+
Stability in body	lower	high
Blood levels	lower	higher and better sustained

CEPHALOGLYCIN AND CEPHALEXIN

Of these two orally administrable cephalosporins, cephaloglycin is poorly absorbed but attains concentrations in the urine adequate for treating infections by enterobacteria, which are very sensitive to it. It is used in the United States but unavailable in Britain. Cephalixin, on the other hand, is the best absorbed of all oral antibiotics; it attains high initial blood levels, with only about 11% protein-bound, and 90% or more of the dose is recoverable from the urine. Against this ease of administration has to be set an antibacterial activity lower than that of injectable cephalosporins on most species (table V). Cephalixin is from four to 17 times less active than cephalothin against Gram-positive cocci; against all but one of these its inferiority to cephaloridine is even more pronounced. The differences among enterobacteria are less, and here we have a single instance of cephalixin superiority; it is resistant to the β-lactamase which confers resistance on some strains of *E. coli* not only to ampicillin but to cephalothin and cephaloridine. The findings for *H. influenzae* are noteworthy. Cephaloridine has poor activity against this organism, and has been reported as failing even in massive doses to eliminate it from the cerebrospinal fluid in three cases of meningitis.¹⁷ The activity of cephalixin is even less, and reliance on it in bronchial infections, in which *H. influenzae* is a common pathogen, appears to be misplaced.

TABLE V—Antibacterial Activity of Cephalosporins

Organism	Minimum Inhibitory Concentration (µg/ml)			
	CT	CL	CX	CX/CT ratio
<i>Staph. aureus</i> (penicillin-sensitive)	0.129	0.043	2.26	17
<i>Staph. aureus</i> (penicillin-resistant)	0.146	0.188	2.06	13
<i>Strept. pyogenes</i>	0.09	0.01	0.58	6
<i>Strept. pneumoniae</i>	0.13	0.03	0.58	4
<i>E. coli</i>	4	2	4	1
<i>Es. coli</i> (ampicillin-resistant)	16	16	4	0.25
<i>Klebsiella</i>	2	2	16	8
<i>Pr. mirabilis</i>	1	2	4	4
<i>H. influenzae</i>	4	8	32	8

CT = cephalothin

CL = cephaloridine

CX = cephalexin

Data for Gram-positive organisms from Kayser¹⁷⁾Data for Gram-negative organisms from Waterworth¹⁸⁾

Cephalexin is mainly used in domiciliary practice, and it is not easy to discover for what purposes it is preferred. In defining what these should be much depends on how far the factor of cost should be taken into account. Many urinary tract infections respond to it, but most of them to other drugs as well; the special indications for cephalexin are infections by ampicillin-resistant *E. coli* and by β -lactamase-forming *Pr. mirabilis*. It should be effective in streptococcal infections, such as acute sore throat, and in pneumococcal infections, but so is penicillin V. For any staphylococcal infection an alternative is one of the isoxazole penicillins. There are thus other antibiotics, equally easy to administer, which serve these purposes, and whether cephalexin gives better results can only be decided by extensive clinical experience.

OTHER CEPHALOSPORINS

A bewildering succession of new derivatives has recently been described, most of which have not yet gained an assured place in clinical use. A virtue claimed for all of them is that they are not nephrotoxic, and for some that they are active against enterobacteria relatively resistant to cephalothin and cephaloridine. Cefazolin^{20, 21} is somewhat superior in activity against *E. coli* and *Klebsiella*, and attains very high and well-sustained blood levels, but is about 80% protein-bound. Superior activity against certain coliforms is also claimed for cefamandole²² and for cephacetrile.²³ Cefamandole also possesses exceptional activity for a cephalosporin against *H. influenzae*.²⁴ The merit of cefoxitin²⁵ is similarly based; this is in fact not a cephalosporin but a cephamycin, with a slightly different nucleus. It has poor activity against Gram-positive organisms, but is resistant to the β -lactamase formed by indole-positive *Proteus* spp. and some strains of *Klebsiella*, which are consequently sensitive to it, though not to cephalothin. The main virtue claimed for cephradine²⁶ is good local tolerance. All these have to be injected; cephradine is administered orally. This product has a structure closely resembling that of cephalexin, and similar activity to it both in vitro and in experimental infections.²⁷

Conclusions

No one wants to stand in the way of progress. When a new derivative of an antibiotic can do something which its predecessors cannot, it should be made available. But if the new activity is only against a rather uncommon and not very important non-specific infection, the manufacturers will not be content to advocate its use for this purpose only. Unless the new drug can find a place among those used in treating respiratory and urinary tract infections generally—the two fields accounting for by far the greater part of antibiotic usage—it has little prospect of commercial success.

The appeal of novelty, reinforced by skilful publicity, should not be underrated, but the very latest thing is not always the best. If it were possible to analyse the purposes for which a new cephalosporin is being prescribed, it would probably be found that many of them would be as well or better served by ampicillin. If the same exercise were undertaken for ampicillin prescriptions some of them would certainly prove to be for purposes well served by penicillin. The large field of urinary tract infections is also served by five different types of synthetic drug, and here there may sometimes be no real need to look to any antibiotic at all.

The choice which is the subject of this lecture may have to be made by the prescriber alone, and if it is made on the basis of comparable past experience it may well be a good one. If he has the help of a painstaking bacteriologist it is more likely to succeed. This helps involves not only identifying the causative organism but verifying its sensitivity to the antibiotic to be used. In Gram-positive infections this is rarely necessary: streptococci and pneumococci may be assumed to be sensitive to any penicillin or cephalosporin, and staphylococci are better assumed to be resistant to penicillin, ampicillin, and phenoxypenicillins unless proved otherwise. With enterobacteria it is different. *E. coli*, for instance, may be resistant to ampicillin, and so will *Pr. mirabilis* if it forms a β -lactamase; as already mentioned, these infections may be indications for cephalexin. Some of the less common β -lactamase-forming enterobacteria may be fully sensitive only to one of the newer derivatives such as cefoxitin. In treating respiratory infections it is important to know whether *H. influenzae* is responsible, since if so most cephalosporins are unlikely to be of much value, whereas ampicillin probably will be. When both clinician and bacteriologist bear facts such as these in mind, treatment will be soundly based and so far as possible assured of success.

The following are trade names by which the principal antibiotics described are known in Britain:

Amoxycillin	Amoxil (Bencard)
Ampicillin	Penbritin (Beecham)
Carbenicillin	Pyopen (Beecham)
Cephalexin	Ceporex (Glaxo), Keflex (Lilly)
Cephaloridine	Ceporin (Glaxo)
Cephalothin	Keflin (Lilly)
Cephadrine	Eskasef (Smith, Kline and French), Velosef (Squibb)
Cloxacillin	Orbenin (Beecham)
Flucloxacillin	Floxapen (Beecham)
Methicillin	Celbenin (Beecham)
Oxacillin	Prostaphlin
Phenethicillin	Broxil (Beecham)
Propicillin	Brocillin (Beecham), Ultrapen (Pfizer)

References

- 1 Florey, H. W., *Proceedings of the Royal Society of Medicine*, 1943-4, 37, 104.
- 2 Behrens, O. K., et al., *Journal of Biological Chemistry*, 1948, 175, 793.
- 3 Bond, J. M., Lightbown, J. W., Barber, M., and Waterworth, P. M., *British Medical Journal*, 1963, 2, 956.
- 4 Garrod, L. P., *British Medical Journal*, 1960, 2, 1695.
- 5 Penicillin V. Panel Discussion, *Antibiotics Annual*, 1955, 6, 950.
- 6 Francis, R. S., and Spicer, C. C., *British Medical Journal*, 1960, 1, 297.
- 7 Francis, R. S., May, J. R., and Spicer, C. C., *British Medical Journal*, 1961, 2, 979.
- 8 Barry, A. L., and Hoeprich, P. D., *Antimicrobial Agents and Chemotherapy*, 1973, 4, 354.
- 9 Tan, J. S., Terhune, C. A., Jun., Kaplan, S., and Hamburger, M., *Lancet*, 1971, 2, 1340.
- 10 Sutherland, R., Croydon, E. A. P., and Rolinson, G. N., *British Medical Journal*, 1970, 4, 455.
- 11 Johnson, D. W., Kvale, P. A., Afable, V. L., Stewart, S. S., Halverson, C. W., and Holmes, K. K., *New England Journal of Medicine*, 1970, 283, 1.
- 12 Brumfit, W., Franklin, I., Hayek, L., and Pursell, R., *Scandinavian Journal of Infectious Diseases*, 1973, 5, 59.
- 13 Sutherland, R., Croydon, E. A. P., and Rolinson, G. N., *British Medical Journal*, 1972, 3, 13.
- 14 Hunter, P. A., Rolinson, G. N., and Witting, D. A., *Antimicrobial Agents and Chemotherapy*, 1973, 4, 285.
- 15 Rodriguez, V., Bodey, G. P., Horikoshi, N., Inagaki, J., and McCredie, K. B., *Antimicrobial Agents and Chemotherapy*, 1973, 4, 427.
- 16 Symposium on Oral Indanyl Carbenicillin in the Treatment of Urinary-Tract Infections, *Journal of Infectious Diseases*, 1973, 127, May Suppl.
- 17 Kayser, F. H., *Postgraduate Medical Journal*, 1971, 47, Feb. Suppl., 14.

- ¹⁸ Waterworth, P. M., *Postgraduate Medical Journal*, 1971, 47, Feb. Suppl., 25.
¹⁹ Walker, S. H., and Collins, C. C., *American Journal of Diseases of Children*, 1968, 116, 285.
²⁰ Bergerson, M. G., Bruschi, J. L., Barza, M., and Weinstein, L., *Antimicrobial Agents and Chemotherapy*, 1973, 4, 396.
²¹ Simon, C., Malerczyk, V., Brahmstaedt, E., and Toeller, W., *Deutsche medizinische Wochenschrift*, 1973, 98, 2448.
²² Eykin, S., Jenkins, C., King, A., and Phillips, I., *Antimicrobial Agents and Chemotherapy*, 1973, 3, 657.

- ²³ Kradolfer, F., Ahrens, T., Gefzer, J., Vischer, W., and Zimmermann, W., *Schweizerische medizinische Wochenschrift*, 1973, 103, 711.
²⁴ Williams, J. D., and Andrews, J., *British Medical Journal*, 1974, 1, 134.
²⁵ Kosmidis, J., Hamilton-Miller, J. M. T., Gilchrist, J. N. G., Kerry, D. W., and Brumfitt, W., *British Medical Journal*, 1973, 4, 653.
²⁶ Bodner, S. J., and Koenig, M. C., *American Journal of the Medical Sciences* 1972, 263, 43.
²⁷ Neiss, E. S., *Journal of the Irish Medical Association*, 1973, 66, 24 March, Suppl., p. 1.

Contemporary Themes

Port Health Control

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Summary

Almost 950,000 of the 21 million passengers passing through London (Heathrow) Airport in 1973 were seen by the health control unit, which is run by the London Borough of Hillingdon. The unit provides 24-hour medical cover and its responsibilities include x-ray examination for tuberculosis and screening passengers from smallpox-infected areas. It is suggested that, in view of changing epidemiological patterns throughout the world, there is a need to modify existing procedures rather than to abandon them. The development of a follow-up system for tracing passengers at risk and improvements in presenting information about health risks to intending travellers are advocated. While such proposals might be opposed, they could be practicable.

The introduction of the practice of quarantine is usually attributed to the authorities of Venice, itself a thriving seaport with extensive maritime trade in the Orient, in the fourteenth century. Certainly the word itself is derived from the 40-day isolation period which was imposed in that city for all persons and goods arriving from potentially infected areas. Presumably the intention was to allow any disease to manifest itself among the travellers before they were generally admitted to the port while at the same time allowing some primitive disinfection of the cargo itself. Since the concept of incubation periods and the nature of the infective process were not then known the period selected probably had religious associations and, indeed, some evidence suggests that the period varied between 30 and 50 days before the practice became firmly established.

The survival of quarantine for close on 500 years is a testimony to its apparent effectiveness in spite of reports that both persons and goods were smuggled away from quarantine stations either temporarily or permanently during the waiting period and there appear to have been criticisms of certain countries (which have their echoes today) for their failure to apply the regulations properly or to allow bribery

and corruption to take precedence over proper administration. Nevertheless, quarantine as a measure of port health control was not abandoned because of these abuses but because it was ineffective against the pandemics of cholera which swept into Europe in the nineteenth century, and because the accelerating pace of travel, together with the increasing emphasis upon international trade, made its restrictions intolerable.

It is ironic that these same factors have caused some to advocate that the international health control measures which were created to replace quarantine should now be completely abandoned. Once again *Vibrio cholerae* (as the E1 Tor biotype) has spread to Europe as well as to regions traditionally thought to be immune from the disease.¹ Cholera has been reported in most North European countries among holiday-makers in recent years, and in Italy in 1973 there was a major outbreak of cholera, serotype Ogawa.² Nevertheless there is no recent evidence that major importations of disease in Britain have occurred as a result of failures by port health authorities. The crucial question at the present time is whether the existing regulations are appropriate to the current epidemiological situation, and it may be helpful to examine their operation at one of the world's largest international airports.

The Health Control Unit—London (Heathrow) Airport

In 1973 nearly 21 million passengers passed through London (Heathrow) Airport, of whom 947,803 were seen by the health control unit. There were an estimated 295,000 aircraft movements. Though there are busier airports elsewhere, the variety of travellers and of passenger movement into London (Heathrow) Airport is unique. The arrival of many passengers direct from smallpox endemic areas is commonplace, and never a day goes by without several regular flights from such countries. This is a quite different pattern from that in Canada, or indeed many North American airports—where passengers have almost invariably passed through London, and been subjected to the stringent control measures which are applied.

The health control unit at Heathrow was established in 1947 and has grown with the airport itself. Expenditure on the unit's activities, which in the financial year 1973-4 was budgetted at £248,860, is reimbursed in full by the Department of Health and Social Security but responsibility for the day-to-day administration of the unit rests with the local

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