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Achievements and problems from the view of a physician

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Penicillin made possible the cure of many common, and also the most serious, infections, such as meningococcal meningitis and bacterial endocarditis, often with few or no sequelae. Endocarditis had been invariably fatal. Semisynthetic penicillins added new dimensions of convenience of administration and a broader spectrum in the presence of many β-lactamases.

A quantum step forward was permitted by the derivatives of cephalosporin C. Specific clinical advances were (1) the opportunity to use these in some penicillin-allergic patients, (2) activity against wider range of Gram-negative bacilli, (3) activity against *Bacteroides fragilis* (cefoxitin), (4) more complete renal excretion after oral cephalosporins than with oral penicillins, and (5) delayed renal excretion.

Major remaining problems limiting β-lactam use are (1) allergy, (2) resistant organisms, (3) relatively poor entry into the cerebrospinal fluid (especially of cephalosporins, (4) some nephrotoxicity, (5) local irritation of veins and tissues during administration, and (6) poor results in patients with agranulocytosis.

Background

The major attribute of penicillins and cephalosporins that has made them the centre of so much attention is their ability to cure many important diseases of man. It is highly unlikely the intense effort that has been directed toward the β-lactam antibiotics would have been made had it not been for the therapeutic implications. However, it should be noted that not all bacterial infections were fatal in the pre-antibiotic era, although the mortality may have been high, the course of the illness long and difficult, and the recovery – when it occurred – incomplete.

One example, probably the only one, of a bacterial infection that was uniformly fatal before the advent of penicillin is bacterial endocarditis. Although most students of this disease would agree there was no spontaneous recovery before the use of penicillin in appropriate doses, there was a minor opinion that perhaps in 1% of cases spontaneous healing would occur (Libman & Friedberg 1948). At that time a diagnosis of endocarditis was essentially a death sentence (Reinhart 1931). Treatment with sulphonamides, even to the point of toxicity, did not cure endocarditis, even though the infecting organism was sensitive to the sulphonamide *in vitro* (Spink & Crago 1939). This, followed by cures with penicillin, established that bactericidal activity was necessary to cure that previously invariably fatal disease.

Meningococcal meningitis was, and still may be, a devasting disease. A recent edition of an American textbook of medicine stated that 'Before the introduction of antibiotics, meningococcal meningitis and meningococcemia were almost invariably fatal' (Beatty & Petersdorf 1970). Figures of survival in meningococcal meningitis in the early part of this century reveal that 31–48% survival in this disease was commonplace then (Wilson & Miles 1961). Unfortunately, devasting injury to the nervous system of the survivors was often present, as in the case of Helen Keller. Unfortunately, most survivors with cranial nerve injury did not fare as well.

Pneumococcal pneumonia was frequently the way older patients left the world, and it was estimated that untreated, the mortality matched the decade of life of the patient (Austrian & Gold 1964), whereas today many patients with this disease need not even be hospitalized.

Achievements of penicillin G

The specific achievements of β-lactam antibiotics, and penicillin G in particular may be summarized as follows:

(1) produced rapid and complete cure of many common bacterial infections, such as group A streptococcal pharyngitis and skin infections, pneumococcal pneumonia, and most staphylococcal infections (when the organism was sensitive);

(2) produced cure – usually complete – of such serious, frequently fatal infections such as meningococcal meningitis;

(3) frequently produced cures, often without residue of a previously invariably fatal infection, bacterial endocarditis, if the causative organism was sensitive, and treatment was initiated early enough.

Table 1. Life expectancy in the United States (years)

group	1977	1939	1900
total population	72.5	63.7	47.3
male	68.7	62.1	46.3
female	76.5	65.4	48.3
white	73.2	64.9	47.6
non-white	67.9	54.5	33.0

Some of the many broader effects of penicillins are:

(1) millions of lives have been saved;

(2) hundreds of millions of infected humans have been spared pain, suffering and discomfort;

(3) the necessity of mastoidectomy after recurrent or chronic middle ear infection has been almost eliminated;

(4) the need for hospitalization has often been completely eliminated, or the duration of stay shortened in many infections;

(5) many individuals have been saved from sterility due to infections of the Fallopian tubes or epididymitis;

(6) *possible* factor in decrease in number of cases of meningococcal meningitis;

(7) *possible* factor in decrease in number of cases of rheumatic fever;

(8) *possible* factor in longer life expectancy.

It should be emphasized that items 1–5 are quite definite, whereas items 6–8 are highly debatable. These latter changes certainly occurred concomitantly with the introduction of penicillins, although in each case there was some or major evidence of the trend's having been established earlier (table 1) (U.S. Department of Health, Education and Welfare 1977). Some observers claim that penicillin had nothing whatsoever to do with these changes. Concerning the prolonged life expectancy, there is good evidence that the most dramatic improvement was related to improvement in sanitation rather than specific advances in medical science. It has been argued that this is a reason that plumbers should be paid more than doctors.

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Achievements of semi-synthetic penicillins

Additional very major achievements were made by the introduction of the semi-synthetic penicillins. The most striking were:

(1) activity against resistant (β-lactamase producing strains) *Staphylococcus aureus*;

(2) decreased need for multiple drugs for *S. aureus* – this permitted treatment with less toxicity and fewer adverse reactions;

(3) broader spectrum, especially against Gram-negative bacilli such as *H. influenzae*, *E. coli*, *Pseudomonas* etc., e.g. by ampicillin, carbenicillin;

(4) permitted synergy via β-lactamase inhibition, both *in vitro* (Sabath & Abraham 1964, Sabath *et al.* 1965) and in patients (Sabath *et al.* 1967); much current work (other papers at this meeting) with new β-lactamase blockers is an extension of this work.

Specific achievements of cephalosporins

The consideration of cephalosporins along with penicillins is most appropriate, because of some similarity in actions and structure. The discovery of penicillin G and its impressive clinical utility obviously stimulated the effort that led to the discovery of the cephalosporins (and also most other antibiotics). Of the more than 5000 cephalosporin compounds prepared, less than a dozen have been extensively used in clinical medicine.

Current antibiotic usage patterns in many American hospitals is such that 15–20 % of the total money spent on drugs of all classes is for cephalosporins! About 33 % of all money spent is for anti-infective drugs, indicating that in some hospitals one-half to two-thirds of all money spent on antibiotics is for cephalosporins. Yet some physicians have even claimed that there is not a single bacterial infection for which a cephalosporin is the 'drug of choice.' One current use about which there is some controversy, that accounts for a large fraction of cephalosporin usage in hospitals, is in prophylaxis against infection associated with various surgical procedures.

Although controversy exists, there are a number of specific achievements of cephalosporins in medicine:

(1) they are useful in some patients allergic to penicillins, especially when there has been a delayed type reaction;

(2) they are active against a wider range of Gram-negative organisms than are most penicillins;

(3) some cephalosporins (especially cefoxitin, and to a lesser extent cefamandole) have activity against some Gram-negative anaerobic organisms;

(4) several of the orally absorbed cephalosporins (especially cephalexin and cephradine) have much more complete renal excretion than any of the orally absorbable penicillins – specifically, only about 30 % of ampicillin ingested appears in the urine; with amoxicillin it may be double that whereas 95–100 % of the two cephalosporins mentioned appear in the urine after oral ingestion;

(5) some of the cephalosporins tend to be more resistant to the inoculum effect;

(6) some have delayed renal excretion (e.g. cefazolin), permitting fewer doses and higher blood levels with a given dose.

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Problems of β-lactam antibiotics

In spite of the impressive achievements of the β-lactam antibiotics, a number of extremely important problems remain limiting their use. The following nine points are the most conspicuous.

(1) Penicillin *allergy*, in its extreme form (anaphylaxis with or without upper airway obstruction) may be fatal, and in its delayed forms (e.g. rash, arthralgia, drug fever, haemolytic anaemia, interstitial nephritis) may be an annoyance or even grossly debilitating. Some considerable debate continues whether there is cross-allergenicity with cephalosporins, or frequent concommitant allergenicity. Estimates of the frequency of penicillin allergy range from 2–5 % of the population to 3–10 %. The current status is that many individuals with serious or life-threatening infections who might benefit from a β-lactam antibiotic are forced to use less desirable alternative antibiotics, or one of these with various degrees of risk or even morbidity. The problem is in need of solution.

(2) *Bacterial resistance* to β-lactam antibiotics was the first major factor limiting their use, and has been an important stimulus in the search for new antibiotics. Resistance due to drug inactivation (by penicillinase) was the first mechanism of resistance noted (Abraham & Chain 1940); virtually all highly resistant organisms, including the tubercle bacillus produce some β-lactamase ('penicillinase'), and the larger amounts available with heavier inocula usually increases the apparent minimum inhibitory concentration (m.i.c.) *in vitro*, thus confounding interpretation of these tests for clinical usefulness. The varying degree of relative resistance to hydrolysis is not the only factor accounting for differences in antibacterial activity of the various β-lactam antibiotics (Sabath & Finland 1967). Resistance not due to drug inactivation is often termed intrinsic resistance and is frequently thought to be mainly a problem of penetrance or access to key binding sites, but relative importance of this probably varies with different organisms. A third form of resistance, probably also of clinical importance is 'tolerance' to the killing action of β-lactam antibiotics (Sabath *et al.* 1977). As noted, without bactericidal therapy, bacterial endocarditis cannot be cured.

(3) *Tissue penetration* of any drug is important and for the β-lactam antibiotics, their relatively poor entry into the cerebrospinal fluid (c.s.f.) and the eye severely limits their usefulness in infections of the central nervous system and the eye. The fact that benzylpenicillin has been so useful in brain abscess, and for meningitis due to *Neisseria meningitidis* and *Streptococcus pneumoniae*, reflects the equisite sensitivity of those aetiological agents to this drug. However, when the m.i.c. is somewhat higher (10-fold to 100-fold) as in *Haemophilus influenzae*, then the relatively poor entry of the antibiotic into the c.s.f. becomes a limiting factor.

(4) *Local tissue irritation* by β-lactam antibiotics manifests itself by pain at site of injection or intravenous (i.v.) infusion, phlebitis after i.v. infusion, and (rarely) sterile abscesses, at site of injection. These problems frequently make administration of drug difficult or impossible, forcing a change of route of administration or even a change of selection of drug. The scientific basis of this tissue irritation has not been conclusively demonstrated as has the reason why some, such as cephaloridine, cause much less pain after intramuscular injection than the others.

(5) *Instability* of most penicillins and cephalosporins in solution or in various bacteriological media has presented more problems than are generally recognized. Some of these β-lactam antibiotics may 'decompose' in solution, meaning that they cannot be prepared very far in advance of the time of i.v. administration. Their instability in various media is not a great

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problem in the testing of most pyogenic organisms, but slower growing organisms such as mycobacteria may not begin showing visible growth for a number of days after inoculation – at which time little or no β-lactam antibiotic may be in the medium. Thus, the apparently high m.i.c. values recorded may not be correct, in view of this instability (Lorian & Sabath 1972).

(6) *Oral absorption* of some highly desirable β-lactam antibiotics (e.g. nafcillin) is so poor or irregular that the informed physician cannot prescribe them in clear conscience, when appropriate drugs with more desirable absorption characteristics are available.

(7) *Nephrotoxicity* of β-lactam antibiotics is receiving more attention. In the past an allergic-type vasculitis was thought to account for most of these cases, but the availability of renal biopsy has made it possible to examine tissue from living patients. It is now clear that many of the β-lactam antibiotics can cause intrastitial nephritis, and it appears this happens more frequently with methicillin than with some of the others.

(8) The effect of the β-lactam antibiotics is '*only antibacterial*' – the main property studied in clinical laboratories. That a 'miracle drug' might do more than that would possibly be asking too much. However, before the introduction of penicillin into medicine it was not known that effectively killing the organism inciting the disease might not be enough. The high morbidity and mortality associated with pneumococcal meningitis is an example of this problem. Obviously, it would be desirable to stop the chain of events causing the disease in addition to eliminating the pathogen.

(9) *Host defence activity*, especially of phagocytic cells such as the polymorphonuclear leucocytes and the macrophage, is needed for the cure of most systemic bacterial infections, even though *in vitro* the antibiotic may be able to kill all of the bacteria over a few days. It is not known why this does not happen in the body, but the frequent failure of antibiotics 'alone' to cure severe infections in patients with agranulocytosis – drug induced or otherwise – illustrates this shortcoming of β-lactam (and other) antibiotics.

Broader problems and advances possibly stimulated by β-lactam antibiotics

Although it would be difficult to prove, the following appear to exist, at least in part, as a result of the availability of penicillins:

(1) increased sexual freedom (less fear of veneral disease);

(2) inter-species transfer of bacterial resistance genes (Sabath *et al.* 1978);

(3) increased knowledge of bacterial physiology;

(4) increased research into the pathophysiology of infection;

(5) increased interest in immunology. Maurois (1969) has reported that Fleming's interest and enthusiasm for penicillin was dampened by the conviction of his chief, Sir Almroth Wright, that immunology and not chemotherapy was 'the answer' to the problem of infection. This is open to question. But it is ironic that some of the shortcomings of antibiotics have rekindled comprehensive research in some areas of immunology.

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