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## Gaps in Therapy for Infectious Diseases: A Historical Perspective

The title of this Symposium—"Gaps in Therapy of Infectious Diseases"—seems quite appropriate for a conference sponsored by Miles Pharmaceuticals—a pharmaceutical manufacturer with essentially no previous experience in the discovery, development, and distribution of new anti-infective agents—as it merges with Bayer A.G.—the German giant in the pharmaceutical industry, which has long been in the forefront of developments in this field, among the many others to which it has made notable contributions.

It is also appropriate that these two companies, as they launch their joint ventures, have gathered this group of distinguished specialists in the application of the results of research and development in the field of infectious diseases. Nearly all of the participants are experienced in the management of patients with infections and have devoted much of their professional talents to the care of such patients. They are therefore only too well aware of gaps in currently available therapy.

As a senior participant here, I have been called on to provide a historical perspective of the gaps in therapy for infectious diseases, which I propose to relate mostly to my personal experiences and involvements, which go back further in time than those of most, if not all, of those gathered here.

From May 29 through June 4, 1981, a group of about 100 infectious disease clinicians, either actively engaged in the investigation of antimicrobial agents currently available or administrators of publicly and privately supported institutions with extensive backgrounds and experience in infectious diseases and their treatment, participated in a symposium entitled "Gaps in Therapy of Infectious Diseases," sponsored by the Miles Pharmaceuticals Division of Bayer A.G. The conference was held sequentially in New York, New York, and Leverkusen, Federal Republic of Germany (the base of Bayer A.G.). The Miles Pharmaceuticals Division will be introducing in the United States, over the next several years, a series of major new compounds for the treatment of infectious, cardiovascular, and metabolic diseases. The initial activity is in the field of infectious diseases, in which Bayer A.G. has experience with major contributions.

This perspective was presented at the symposium in New York City on May 30, 1981.

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## The Modern Chemotherapeutic Era

*Paul Ehrlich.* Before turning to my own early experiences, I would like to refer to Paul Ehrlich, the generally acknowledged father of modern chemotherapy, to some of his early work, and to the far-reaching principle that he promulgated. Ehrlich thought of chemotherapeutic drugs in terms of their capability of reacting with chemoreceptors, on or in the parasite (parasitotropic), rather than with sites in or on the host cells (organotropic). He committed himself to the task of altering the structure of toxic substances so as to change the therapeutic ratio, by increasing the parasitotropic and decreasing the organotropic activity of these chemicals, and thus producing a favorable "therapeutic index."

Starting with arsenical compounds that already had proved successful in the treatment of trypanosomiasis in horses, he and his colleagues proceeded to synthesize aniline derivatives. By 1932 at least 12,500 organic arsenicals had been produced based on a *p*-aminobenzyl nucleus. Among the most important were *p*-aminophenyl arsenoxide, which proved to be active against trypanosomiasis, and later arsphenamine, which was the mainstay of the treatment of syphilis, relapsing fever, and trypanosomiasis for many years until penicillin was discovered.

*Development of sulfonamides.* One can readily discern the parallelism with the later development of sulfanilamide derivatives in which the sulfonamide moiety replaced that of the arsenical. Numerous aniline dyes with related structures had been synthesized before Gerhard Domagk at I. G. Farbenindustrien (now Bayer's chemical division) produced Prontosil<sup>®</sup>, the one that proved to be active against streptococcal infections, and its activity was shown to reside in the *p*-aminobenzene sulfonamide (sulfanilamide) which it liberated in the body and which was identified in the urine. Within two or three years of this revelation, several thousand derivatives of sulfanilamide were synthesized and tested for their antibacterial and therapeutic activity. Among them, however, only a limited and small number was tested in humans

and made their way into the therapeutic armamentarium for the treatment of infectious diseases in humans.

Prominent among the early derivatives with which I and others had to deal were the succession of sulfapyridine, sulfathiazole, and sulfadiazine and its monomethyl and dimethyl derivatives. Each of them left a gap in therapy. Sulfapyridine induced severe gastrointestinal side effects; sulfathiazole produced frequent and sometimes life-threatening allergic reactions, some of which, such as erythema nodosum, episcleritis, severe urticaria, and even hepatitis with jaundice, were unique. Both of these compounds and the sulfapyrimidines (sulfadiazines) produced drug fever, drug rashes, crystalluria, and hematuria—the last of these related to the insoluble and generally inactive acetyl derivatives which were excreted in various proportions into the urine. The latter “gap” (that is, the unwanted crystalluria and hematuria) was bridged by combining the three diazine derivatives as trisulfapyrimidine; the combination was used successfully because each of the derivatives was excreted as a compound with its separate solubility, and crystalluria did not occur from use of the mixture. Later, sulfisoxazole and sulfamethoxazole achieved wide acceptance; the former produced little or no crystalluria and the latter was excreted more slowly and, more recently, was combined with trimethoprim in a widely and successfully used fixed combination.

Several other sulfonamides achieved wide use for special purposes or were preferred because of special pharmacokinetic or therapeutic properties useful in certain specialties: phthalylsulfathiazole and succinylsulfathiazole because of their poor absorption from the intestine, mafenide and silver sulfadiazine for the topical treatment of burn wounds, *N*<sup>1</sup>-acetylsulfanilamide for ophthalmologic disorders, and several others for their prolonged action and excretion into the urine. A number of others could be mentioned, but these examples should suffice to illustrate how each useful compound was meant to fill some gap in therapy; however, other gaps remained, were created, or developed in the course of their use—notably, resistance of many bacteria to their action.

*Antibiotics: discovery and cost.* Among the antibiotics, the penicillins and cephalosporins are the prime examples of the use of chemical modifications of a core nucleus to alter their phar-

macokinetics as well as their spectrum and degree of antibacterial activity and their potential for influencing the production of inactivating enzymes or for resisting their action. However, the sensitizing property—the potential for producing drug fever, rashes, and other allergic reactions—has not yielded to the guiles of the chemists and pharmacologists, thus leaving an important gap. The chemists have had more limited success in producing large numbers of useful modifications to fill gaps in the activity, pharmacokinetics, and toxicity of other classes of antibiotics—the macrolides and the related lincomycins, the aminoglycosides, the tetracyclines, and particularly chloramphenicol and the polypeptides, including the polymyxins. Several chemical agents of a new class have found limited acceptance and have been used alone or in combinations with other antibiotics to fill some gaps in therapy: fusidic, nalidixic, oxalonic, and clavulanic acids are the prime examples, and the last of these has even proved to be harmful when used in some combinations.

The cost of discovering and developing a useful new drug to the point of marketing and acceptance in the United States is now estimated at between 20 and 60 million dollars. A manufacturer must, therefore, be convinced of the presence of a real gap in therapy and of the marketing potential of any newly discovered agent or even a modification of an approved and useful one to warrant the large investment required for developing it to its full potential.

This sketchy review has touched only on chemotherapy—that is, the treatment with biosynthetic, semisynthetic, or synthetic chemical entities—and has skipped right through some of the major elements of the modern chemotherapeutic era that are really the domain of the other essayists and discussants. They, in turn, will point out the gaps in the currently available therapeutic armamentarium against infections.

#### **Recollections on the Elimination of Gaps in Therapy for Infectious Diseases**

Now, I would like to take you back to my earliest interests and point out some of the gaps in therapy for infectious diseases that my contemporaries and I encountered in the days before anti-infective chemotherapy, when the principal reliance was on biologic products—namely, antisera produced in animals (mostly in horses but later also in rabbits

or other animals and to a small extent also in humans) for treatment of specific infections—and vaccines of whole bacteria or their products for protection against such infections.

When I began my internship on one of the medical services at the Boston City Hospital more than half a century ago, the most frequent serious infection among patients on our medical wards was pneumonia, mostly pneumococcal in origin. At that time and in the preceding decade, there had been a certain amount of investigation into the action of quinine and certain of its derivatives on pneumococci in vitro, on the therapy for experimental pneumococcal infection (mostly in mice), and, to a limited extent, on the therapy for pneumococcal pneumonia in humans. This research culminated in the development of ethylhydrocupreine, which had been the subject of some clinical trials. However, the evidence for its usefulness was conflicting. Its immediate effect on fever and “toxicity” was favorable, but it was without effect on bacteremia, empyema, or meningitis and produced undesirable effects, mostly neurologic. Hydroxyethylhydrocupreine and other derivatives were somewhat less toxic and were the subjects of limited clinical trials, but failed to gain any wide acceptance. The only residual of that flurry of interest is the optochin (ethylhydrocupreine) disk, which is still used in many clinical laboratories to differentiate colonies of pneumococci (which are sensitive) from those of  $\alpha$ -hemolytic streptococci (which are not).

*Antiserum for pneumococcal pneumonia.* The only specific therapy available for treating patients with pneumonia when I first came on the wards was the iv administration of unconcentrated antiserum to type I pneumococci. A review of the results achieved at Boston City Hospital up to the time that I finished my internship clearly demonstrated that this antiserum was effective in reducing mortality, controlling and reducing the period of fever and severe illness, and preventing pyogenic complications (mostly empyema), but only among patients receiving large amounts (200–600 ml) and whose treatment was begun within three days of the onset of the disease as we were able to define it on clinical grounds. Because injections of large amounts of the unconcentrated horse sera that were then available frequently entailed immediate and delayed reactions of varying degrees of severity and were associated with considerable discomfort, it was imperative to limit such therapy

to patients with pneumonia due to type I pneumococci and to start therapy as early as possible after the onset of the disease. Such patients generally accounted for less than one fifth of those with classic signs of pneumococcal lobar pneumonia. To treat all of the patients who had lobar pneumonia promptly on admission would have meant subjecting at least four patients to the hazards of the therapy who would not be expected to derive any benefit for every one who might be helped. Therefore the initiation of therapy was delayed until the pneumococcus could be demonstrated and its specific type determined and shown to be type I. Thus we have the first gap in such therapy—namely, the delay in specific diagnosis.

*Identification of specific types.* The method used at that time for the typing of pneumococci from patients with pneumonia involved ip injection of properly obtained sputum into a mouse, which usually died overnight or after  $\sim 24$  hr. Peritoneal exudate obtained from the dead or moribund mouse was diluted, mixed in small tubes with types I, II, and III typing sera, incubated at 37 C, and observed for type-specific agglutination. A drop of the mouse’s cardiac blood, obtained with sterile precautions and cultured on blood agar and in blood broth, usually yielded the pneumococcus in pure culture and confirmed the diagnosis. It was at about this time that Albert Sabin, then a medical student at New York University in New York City where he spent a good deal of time working in the bacteriology laboratory of Dr. William H. Park, developed the Sabin test. This test involved removing a few drops of peritoneal exudate with a capillary pipette from the live, infected mouse 3 or 4 hr after inoculation and mixing one drop separately with antiserum to each of the three pneumococcal types on a slide, Gram-staining, and examining smears of the stained mixtures microscopically. The specific type could be recognized by the clumping of the dark blue-staining pneumococci surrounded by the uniformly red-staining material that involved the capsule and the specific antigen-antibody precipitate. The mixtures of exudate and heterotypic sera showed the pneumococci uniformly distributed. The agglutination could usually be recognized during the mixing or by gross inspection of the smears [1].

The gap in time required for specific typing was further narrowed when Sabin was serving as an intern at Bellevue Hospital in New York City. At

that time, Kenneth Goodner had returned from a visit to F. Neufeld's laboratory where he saw a demonstration of the "Quellung" (capsular swelling) reaction of pneumococci mixed with specific antisera prepared in rabbits, which Neufeld had described many years earlier [2]. Sabin applied the method to freshly collected sputum from his patients and, after demonstrating its utility, published the details of the method [3]; it came to be known as the Neufeld (Quellung) method and has served as the most useful and rapid method for typing pneumococci. By this method the type can be accurately determined directly from properly collected fresh sputum in a few minutes and thus permits prompt institution of specific therapy as soon as the clinical diagnosis is made. The method is, of course, equally and even more readily adapted to typing directly from blood cultures or infected exudates, even if the organisms are not viable.

Another diagnostic gap to be filled was for patients who could not raise sputum. Dochez and Avery had demonstrated type-specific polysaccharide in the blood and urine of patients acutely ill with pneumococcal pneumonia [4] by overlaying the patient's serum or urine with specific antisera and observing a precipitate at the junction. The method has since been refined by immunodiffusion and electrophoretic methods. Conversely, a retrospective type diagnosis could be made by the use of convalescent-phase serum from the patient in similar tests with specific polysaccharide antigens. This method, which was not widely used in clinical laboratories, is also applicable to quantitation of type-specific antibodies present in convalescent-phase serum or raised by immunization with specific capsular polysaccharide vaccines [5].

*Concentrated antibodies to pneumococci.* The large volumes of serum required and the untoward reactions they produced offered another challenge and a gap, the filling of which was tackled by attempts to concentrate the specific immunoglobulin fraction. Methods were developed at Harvard Medical School in Boston by Lloyd D. Felton, at the Massachusetts Antitoxin and Vaccine Laboratory in Boston by Benjamin White and his associates, at the New York City Laboratories under Dr. Park, and at the New York State Laboratory in Albany by Augustus Wadsworth and his staff. These concentrated specific antisera permitted administration of a full course of therapy in 20–40 ml. Reactions to the early lots of

these concentrated antisera, other than those due to sensitivity to horse serum, consisted of severe chills (usually after about an hour) followed by an increase in fever that lasted several hours. For a long time, this pyrogenicity of various lots of antiserum could be determined only by administering the serum to patients. That gap was later to be filled by development of the "pyrogen test," which involves injecting the finished product iv into a group of rabbits and recording their temperature; unsatisfactory (pyrogenic) lots were then reprocessed.

The types and duration of the manifestations of serum sickness were also reduced when concentrated antibody was used. The unconcentrated serum produced prolonged and recurrent bouts of fever, rashes, and severe arthralgias in various combinations, sometimes for several weeks; the separate bouts were attributed to reactions to the different serum proteins. The concentrated sera reduced the duration and multiplicity of these reactions.

Still another gap was filled when therapeutic antisera were prepared against pneumococci of types other than type I. At first antibody to type II and type I pneumococci was combined. Later, as new types were identified, largely by Georgia Cooper in the Laboratory of the New York City Department of Health and subsequently by others, diagnostic antisera were developed for these types, and still later therapeutic sera were prepared and used to some extent against some of them. Subsequently, the production of more concentrated therapeutic antisera prepared in rabbits greatly extended the therapeutic range and efficacy while reducing somewhat further the frequency and severity of untoward reactions.

*Antisera for nonpneumococcal infections.* In addition to pneumococcal pneumonia, another serious and not uncommon infection with which my medical contemporaries and I were confronted was meningococcal meningitis, and my pediatric colleagues (at Children's Hospital in Boston) were also attempting to cope with highly fatal meningitis due to *Haemophilus influenzae* type b. Gaps in therapy for each of these infections were partly filled by specific antisera. For meningococcal meningitis, only unconcentrated antisera (to the then known types) were available and, like the corresponding antiserum to type I pneumococci, had to be given iv in similarly large doses, with small amounts also being injected intrathecally.

This therapy increased the recovery rate from meningococcal meningitis from ~20% in untreated patients to 40%–60% in patients who were treated early in the disease, but, in addition to the severe serum sickness that followed among patients who recovered, permanent and complete blindness and deafness were frequent, especially in infants and young children. Later, antiserum to *H. influenzae* type b produced in rabbits was used with some success.

Just before sulfanilamide and its derivatives became available and proved to be remarkably successful in rapidly curing meningococcal meningitis, the Laboratory of the New York State Department of Health produced antiserum to meningococci that William Tillett used at The Johns Hopkins Hospital in Baltimore and reported 25 recoveries in 26 consecutively treated patients with meningococcal meningitis [6]. Good results were also being reported in cases of meningitis due to *H. influenzae* type b at Children's Hospital in Boston and Babies' Hospital in New York City. The sulfonamides and later the antibiotics rapidly rendered these antisera obsolete and further narrowed the gaps in the treatment of these infections. Moreover, pneumococcal meningitis, against which specific antisera were totally ineffective and which had been universally fatal, also responded favorably to therapy with sulfonamides and antibiotics, yielding a recovery rate of  $\geq 70\%$ , thus narrowing still another gap in therapy.

I recall in 1939 visiting with the late Dr. Wilbur G. [Weed] Malcolm, then Director of Lederle Laboratories in Pearl River, N.Y., who took me to a huge refrigerated room lined with shelves that were loaded with carboys full of unconcentrated sera from some 75,000 rabbits that had been fully immunized against pneumococci of all of the frequently occurring types. He was at a loss to know how to dispose of this treasure, which he was willing to give away; he eventually discarded nearly all of it.

*Vaccines.* Efforts had also been made to develop vaccines to protect against pneumococcal infections. At first, whole pneumococci of the first known types (I, II, and III) were used. Later, mixtures of other types that had been encountered in South Africa, where pneumonia was endemic and caused much illness and considerable mortality, were used. These vaccines met with only temporary and limited success. Subsequently, purified type-specific polysaccharides of individual types

were used successfully to halt institutional outbreaks of pneumonia, and a polyvalent polysaccharide vaccine showed some effect in reducing pneumonia rates in military units. Efforts to perfect and extend the use of these vaccines were revived, largely by Robert Austrian at the University of Pennsylvania in Philadelphia in collaboration with Maurice R. Hilleman of Merck Sharp and Dohme Research Laboratories in West Point, Pa. These efforts resulted in the development of a quatordecavalent vaccine covering 80% of currently occurring types that cause serious pneumococcal infections. These vaccines have proved effective in eliciting antibodies and providing protection against infections due to the same types. With the marketing of this vaccine, still another gap was partly bridged [7].

Vaccines to protect against meningococcal infections have been perfected more recently and are available for types A and C but not for type B or other less common types, thus still leaving a gap. A vaccine that is protective against *H. influenzae* type b also appears to be effective, but its efficacy and safety must still be proved before it is made generally available. An effective vaccine against this organism would be very useful to protect contacts, particularly infants and young children, who have been exposed to others with this form of meningitis or to carriers of that organism. This gap still remains to be closed.

I might mention here the early developments of diphtheria and tetanus antitoxins, first made available as unconcentrated horse sera. These early sera gave rise to reactions similar to those to other unconcentrated horse sera. Concentrated immune globulin of such antisera improved that aspect. However, although still used in acutely ill and toxic patients, these therapies were rendered largely unnecessary and obsolete by the availability of effective antibiotics and in particular by the wide use of protective toxoid vaccines, which have proved highly effective. To these two toxoids has been added pertussis antigen, and triple vaccine (diphtheria, tetanus, and pertussis) has received wide acceptance. In fact, the use of the triple vaccine has become a necessary procedure and, in most states, is required before children are admitted to public schools. It is also of interest that specific phage infection of diphtheria and tetanus bacilli had been found to be essential for the virulence and optimal toxin production by these organisms.

### Persisting General Gaps

Two important general gaps remain in therapy for infectious diseases. One is the need for more reliable methods for selecting the most appropriate therapeutic agent(s) for initiating therapy—that is, for approximating, with a high degree of probability and reliability, the causative infective agent before it is established in the laboratory. The second is the prompt and reliable recognition of the features in the host that must be taken into account in selecting the optimal safe and effective therapy for the individual patient.

### Physician Use of Miracle Drugs

Before closing I would like to refer to statements or claims made by highly respectable scientists who were offering suggestions for filling some gaps in therapy for infections.

Soon after his discovery of streptomycin, Selman Waksman gave the opening address to an antibiotic symposium in which, off the record, he suggested, in effect, that now that penicillin and streptomycin were available, a physician who is called about a patient ill with a fever would promptly prescribe penicillin. If the patient was not improved, the physician would add streptomycin, and if after another day the patient was still sick and febrile, the physician would go to see the patient and try to find out what is wrong—that is, to make a diagnosis. Perhaps such a statement might be excused as a reflection of enthusiasm on the part of a scientist who was not a physician or perhaps it was made only in jest.

Under the heading “Some Unresolved Problems Involved in the Use of Antibiotics,” Waksman later enumerated many such problems in the discovery of organisms that produce antibiotics, the mechanisms of their action, and the type, efficacy, and range of activity and of the reactions they produce. He ended this section as follows [8].

The physician can no longer depend on a “bedside manner.” He must have a well equipped laboratory at his disposal. He must be familiar not only with the antibiotic to be used in each particular patient, but also its concentration [*dose*], frequency of administration, and the reactions of the patient. The doctor must become more than ever before, a scientist, who studies the interaction between the host and the invading organism, learning how to control the latter, without injuring the former [*shades of Ehrlich!*]. Only then can man derive full benefit

from the miracle drugs,—miracles contributed by the harmless microbes for the control of the injurious ones.

Another Nobel Laureate, Sir Ernst B. Chain, at a symposium held in London on the occasion of the 25th anniversary of the first clinical use of penicillin, ventured to suggest that the long, time-consuming, and laborious efforts to roam around the world to seek out compost piles and soil samples for the isolation of microorganisms that might produce useful antibiotics have now become unnecessary and wasteful of time, energy, and expense. Now that the chemical structure of the nucleus of penicillin (and of cephalosporin) has been defined, he suggested that it is necessary only to put the chemist to work to synthesize new derivatives and to call on the pharmacologists and clinicians to evaluate their effectiveness and usefulness in the treatment of infections. The large number of new semisynthetic penicillins and cephalosporins that has been developed in recent years and is still coming forth has certainly extended their range of effectiveness and provided some justification of Dr. Chain’s prediction for filling some of the gaps in therapy for infectious diseases.

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### **Gaps in Therapy for Infectious Diseases: Conference Summary**

This summary reflects the views and the discussion that took place at both sites of the Conference entitled "Gaps in Therapy of Infectious Diseases"—the United States and the Federal Republic of Germany.

In his opening remarks, Dr. George G. Jackson of the University of Illinois Medical Center in Chicago, presiding at the symposium in New York City, indicated that the purpose of the conference was to identify gaps in therapy for infectious diseases in three major areas: bacterial infections, fungal infections, and parasitic infections. Dr. Jackson pointed out that gaps are almost always multiple and outlined certain aspects that are common to each of the three major areas (table 1). (1) Infections may be unresponsive owing to the unavailability of any effective drug for treatment, or infections may be unresponsive owing to an inherent or acquired resistance to drugs that are available. (2) Gaps in therapy may be related primarily to the inability to make an accurate diagnosis of the disease condition in spite of the availability of effective therapeutic agents; new technology for more prompt disease recognition might make presently available drugs more effective. (3) There may be gaps in therapy that are due to the limited period for decisive treatment of the disease; this time limitation may be so critical as to nullify the potential of even highly effective drugs under other circumstances. (4) Drugs that are effectively microbicidal may fail to close a gap in therapy because of inadequacies in pharmacokinetic properties or because of the inability of the host to repair the lesion in spite of antimicrobial drugs. (5) The

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newest developments in the field that have closed recent gaps in therapy or have the potential to do so and the most promising areas of development for the future merit additional consideration.

Dr. Maxwell Finland of Boston City Hospital provided an historical perspective of the last 50 years of chemotherapeutic research, with particular emphasis on his own experiences during that time at Boston City Hospital. Dr. Finland recalled the gaps in therapy for infectious diseases with which he personally became familiar in the treatment of patients with pneumococcal pneumonia using type-specific antisera. Before one could use the available unconcentrated antiserum to type I pneumococci in therapy, one first needed to establish that the patient was infected with type I pneumococci. This confirmation required a time-consuming neutralization test which was carried out in mice. Thus, the first gap in therapy was clearly the delay in establishing a specific bacteriologic diagnosis. This gap was at least partially closed with the development of the Neufeld (Quelling) test, which enabled investigators to identify the specific capsular type of the infecting pneumococcus by direct observation of capsular swelling. The subsequent introduction of sulfonamides, penicillins, cephalosporins, and the other classes of antimicrobial agents began to close a variety of other gaps that existed. Dr. Finland suggested that the two broad gaps that exist in chemotherapy for infectious diseases today lay in methods (1) to optimize initial therapy and (2) to determine defects in the host that permit infectious diseases to develop and progress. The cost of development of a new drug in the United States currently varies from 20 to 60 million dollars; clearly, a decision to develop a new antimicrobial drug is one that is not made lightly.